

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207916Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: January 28, 2016
From: Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: CMC Review #1 of NDA 207916

Subject: Final Approval Recommendation

At the time when the CMC Review #1 was written, the label/labeling issues were not completely resolved. Because of these deficiencies the NDA was not recommended for approval from the ONDP's perspective.

Label/Labeling

On January 28, 2016, revised package insert and carton labels were submitted, and on January 27 2016, revised blisters labels were submitted also, which are acceptable from the CMC perspective except for the new dosage form nomenclature, *effervescent tablets for oral solution*. This was consulted to LNC and deemed acceptable. (see the **Attachment-2**)

The finalized package insert, blisters labels and carton labels are attached. (see the **Attachment-1**)

On November 6, 2015, the OPF has made an overall "approval" recommendation for the drug substance and drug product manufacturing facilities. However, it was noted that the Facility Review section on p. 82 – 83 has a couple of typos for the name of drug substance, and these were clarified via a memo prepared by the OPF reviewer. (see the **Attachment-3**)

Recommendation:

This NDA is now recommended for APPROVAL from the ONDP perspective, with an expiration dating period of **24 months**.

Application Technical Lead

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
1/28/2016

Hitesh N.
Shroff -S

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Date: 2016.01.28 21:19:59 -05'00'

Attachment 1: Finalized labels and labeling

1. Package Insert

(a) “Highlights” Section

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CETYLEV™ safely and effectively. See full prescribing information for CETYLEV.

CETYLEV (acetylcysteine) effervescent tablets for oral solution
Initial U.S. Approval: 1963

-----DOSAGE FORMS AND STRENGTHS-----

Effervescent tablets: 500 mg and 2.5 grams (3)

(b) “Full Prescribing Information” Section

#3. Dosage Form and Strength

3 DOSAGE FORMS AND STRENGTHS

CETYLEV effervescent tablets are supplied as white, round, flat tablets with a lemon mint flavor in the following dosage strengths:

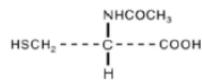
- 500 mg tablets debossed with “T” on one side.
- 2.5 gram tablets debossed with “O” on one side.

CETYLEV tablets contain the inactive ingredient sodium bicarbonate which may be clinically relevant in some patients [see *Use in Specific Populations (8.6), Description (11)*].

#11. Description

11 DESCRIPTION

Acetylcysteine is an antidote for the treatment of acetaminophen overdose. It is the N-acetyl derivative of the naturally-occurring amino acid, cysteine. Acetylcysteine is a white crystalline powder that is freely soluble in water, alcohol, practically insoluble in chloroform and in ether with the molecular formula C₃H₉NO₃S, a molecular weight of 163.2, and chemical name of N-acetyl-L-cysteine. Acetylcysteine has the following structural formula:



CETYLEV (acetylcysteine) effervescent tablets for oral solution contain 500 mg or 2.5 grams of acetylcysteine. The following are inactive ingredients: sodium bicarbonate, maltodextrin, lemon flavor, sucralose, peppermint flavor, and edetate disodium.

The amount of sodium in each tablet of CETYLEV is shown in Table 3.

Table 3: Amount of Sodium Per CETYLEV Tablet

Tablet Strength	Sodium Bicarbonate (mg)*	Sodium (mg)	Sodium (mEq)
500 mg	320 mg	88 mg	3.8 mEq
2.5 grams	1600 mg	438 mg	19 mEq

*inactive ingredient

#16 How Supplied/storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

CETYLEV effervescent tablets are supplied as white, round, flat tablets with a lemon mint smell packaged in 2-count peelable foil blister packs in the following dosage strengths:

- 500 mg tablets debossed with "T" on one side; Each carton containing 2-count blister packs (24338-700-02)
 - NDC 24338-700-05: 5 pack carton containing 10 tablets
 - NDC 24338-700-10: 10 pack carton containing 20 tablets
- 2.5 gram tablets debossed with "O" on one side; Each carton containing 2-count blister packs (24338-725-02)
 - NDC 24338-725-05: 5 pack carton containing 10 tablets
 - NDC 24338-725-10: 10 pack carton containing 20 tablets

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature.] Protect from moisture. Store tablets in original blister package until use.

Dilutions of acetylcysteine should be used freshly prepared and utilized within two hours.

Attachment 2: Concurrence from LNC

Shroff, Hitesh

From: Lostritto, Richard T
Sent: Thursday, January 21, 2016 11:00 AM
To: Shroff, Hitesh
Cc: Mille, Yana R; Rhee, Moo Jhong
Subject: RE: NDA 207916 - Labeling Question for LNC

Follow Up Flag: Follow up
Flag Status: Flagged

The monograph: aspirin "effervescent tablets for oral solution" is in the USP. So there is a precedent:

<http://www.uspnf.com/uspnf/pub/index?usp=38&nf=33&s=2&officialOn=December 1, 2015>

Aspirin Effervescent Tablets for Oral Solution

» **Aspirin** Effervescent Tablets for Oral Solution contain **Aspirin** and an effervescent mixture of a suitable organic acid and an alkali metal bicarbonate and/or carbonate. Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of **aspirin** (C₉H₈O₄).

Also from page 34 of the USP Nomenclature Guideline, see:

http://www.usp.org/sites/default/files/usp_pdf/EN/2014-12-01_nom_guidelines.pdf

If a Tablet for Oral Solution contains components, usually citric acid or tartaric acid and carbonates or bicarbonates, to produce an effervescent solution for oral administration, the name shall be [DRUG] Effervescent Tablets for Oral Solution.

So I think you are on safe ground. I would recommend that tablet in this be pluralized to tablets to fully comply with the dosage form name.

Thanks,
Rik

Attachment 3: A memo from the OPF reviewer.

Arbor Pharmaceuticals, LLC
NDA 207916, Acetylcysteine Tablet

Date January 28, 2016

From Juandria Williams, PhD
Facility Reviewer
Division Inspectional Assessment (DIA)
Office of Process and Facilities (OPF)
Office of Pharmaceutical Quality (OPQ)

Subject Revision of Drug Substance Facility Conclusion Statement for NDA 207916

To Moo Jhong Rhee, PhD Branch Chief, Office of New Drug Products (ONDP)/Branch V

The Division of Inspectional Assessment would like to correct the "Assessment of Facilities" section for NDA 207916 originally signed November 6, 2015. The review conclusion statement for each drug substance facility should read as follows:

Drug Substance Facility	Review conclusion
(b) (4)	This facility is considered acceptable to manufacture the acetylcysteine bulk API to support NDA 207916.
	This facility is considered acceptable to test the acetylcysteine bulk API to support NDA 207916.
	This facility is considered acceptable to test the acetylcysteine bulk API to support NDA 207916.

Please note that the review and the overall recommendation remain unchanged. The drug substance facilities remain acceptable to support NDA 207916.

If you have any questions, please contact me at (301) 796-4916 or by email at juandria.williams@fda.hhs.gov

Juandria Williams, PhD
Facility Reviewer

<table cellspacing=0 width="1100" > <tr><td style="text-align:left;font-family:Times New Roman;font-size:25px;font-style:normal;font-weight:bold;color:#000080;white-space:nowrap" class="TitleCell"> Facility Alerts</td></tr> <tr><td style="text-align:left;font-family:Times New Roman;font-size:25px;font-style:normal;font-weight:bold;color:#000080;white-space:nowrap" class="TitleNameCell" tabindex="0"><label></label></td></tr> <tr><td style="font-family:Microsoft Sans Serif;font-size:11px;color:#8055B7;" class="SubtitleCell"> This report displays the Alerts associated with facilities on the selected applications</td></tr> <tr><td style="text-align:left;border-style:none;border-bottom:solid 1px #7f7f7f;font-family:Microsoft Sans Serif;font-size:10px;color:#000080;" class="SubtitleCell"></td></tr></body> </table> <style type="text/css"> td.ResultLinksCell { } </style>
 <div align="center"> No active OAI / POAI Alerts are present against the facilities on selected Projects</div>

Facility Status View for NDA 207916 Original 1

Displays information for the facilities that are associated to NDA 207916 Original 1. It also shows the Overall Manufacturing Inspection Recommendation for the application and the associated OPF Facility Recommendations.

Time run: 12/14/2015 12:40:01 PM

Overall Manufacturing Inspection Recommendations for NDA 207916 Original 1

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Task Completion Date
NDA 207916-Orig1-New - Form 3674 - User Fee/NDA - Coversheet(2)	ARBOR PHARMACEUTICALS LLC	Approve	Complete	11/6/2015

OPF Facility Recommendations for Facilities on NDA 207916 Original 1

Project Name	FEI	DUNS	Facility Name	Profile	OPF Facility Recommendation	OPF Facility Recommendation Task Status	OPF Facility Recommendation Task Completion Date
NDA 207916-Orig1-New - Form 3674 - User Fee/NDA - Coversheet(2)			(b) (4)	CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	7/17/2015
NDA 207916-Orig1-New - Form 3674 - User Fee/NDA - Coversheet(2)	3004311700	481608818	ALPEX PHARMA SA	TCM TABLETS, PROMPT RELEASE	Approve Facility	Complete	11/6/2015
NDA 207916-Orig1-New - Form 3674 - User Fee/NDA - Coversheet(2)			(b) (4)	CSN NON-STERILE API BY CHEMICAL SYNTHESIS	Approve Facility	Complete	7/17/2015
NDA 207916-Orig1-New - Form 3674 - User Fee/NDA - Coversheet(2)				CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	11/6/2015

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QUALITY ASSESSMENT



Recommendation: This (505)(b)(2) application is **not** deemed ready for approval as of this review in its present form, per 21 CFR 314.125(b)(6).

NDA 207916 Review # 1

Drug Name/Dosage Form	Acetylcysteine effervescent tablets
Strength	500 mg and 2.5 g
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Arbor Pharmaceuticals, LLC, Atlanta, GA
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	March 30, 2015
Amendment	March 30, 2015
Amendment	April 10, 2015
Amendment	July 17, 2015
Amendment	August 14, 2015
Amendment	September 1, 2015
Amendment	September 9, 2015
Amendment	September 11, 2015
Amendment	September 23, 2015
Amendment	October 5, 2015
Amendment	October 6, 2015
Amendment	October 14, 2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Xavier Ysern	OPQ/ONDP/NDAPI/Branch I
Drug Product	Hitesh Shroff	OPQ/ONDP/NDAPII/Branch V
Process	Vaikunth Prabhu	OPQ/OPF/DPAIL/PAB
Microbiology	Vaikunth Prabhu	OPQ/OPF/DPAIL/PAB
Facility	Juandria Williams	OPQ/OPF/DIA/IABIII
Biopharmaceutics	Mei Ou	OPQ/ONDP/DB/BBII
Regulatory Business Process Manager	Anissa Davis	OND/ODEIII/DGIEP
Application Technical Lead	Hitesh Shroff	OPQ/ONDP/NDAPII/Branch V
Laboratory (OTR)	N/A	N/A
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Rannan Bloom	OPQ/ONDP

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	Holder	Item Referenced	Status ¹	Date Review Completed	Comments
(b) (4)	Type II			Acceptable	27-Apr-2015	LOA 22-Oct-2014
	Type IV			N/A	N/A	N/A
	Type III			N/A	N/A	N/A

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMD did not need to be reviewed.)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	13601	MUCOMYST, Apothecon Inc. Division of BMS, NJ, Withdrawn This submission relies on the FDA's previous findings of safety and effectiveness for the listed drug MUCOMYST.

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product.

The Office of Facility and Process has made a final overall manufacturing Inspection "Approval" recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

However, the label/labeling issues have *not* been completely resolved as of this review.

Therefore, from the OPQ perspective this NDA is not deemed ready for approval at this time in its present form per 21 CFR 314.125(b)(6) until the above issues are satisfactorily resolved (see the List of Deficiencies on p. 144)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

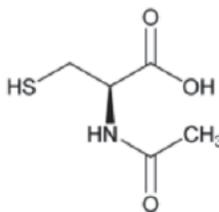
N/A

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

The active pharmaceutical ingredient in the drug product is Acetylcysteine, USP. It is manufactured by (b) (4). The CMC information is provided in DMF (b) (4). The applicant provided an LoA to reference DMF (b) (4) for CMC information. The DMF was reviewed on April 27, 2015 and found to be adequate.

Acetylcysteine, USP is a white crystalline powder. Its chemical name is N-Acetyl-L-Cysteine. Its molecular weight is 163.2 g/mol and molecular formula is C₅H₉NO₃S. The structural formula of acetylcysteine is the following.



It is freely soluble in water and alcohol, soluble in acetone and practically insoluble in methylene chloride and ether. It is not hygroscopic and no polymorphs forms are reported in Eur. Ph. and USP. It is manufactured as a (b) (4) crystalline form. It is an optically pure L-enantiomer synthesized from the natural L-cysteine amino acid.

The API, acetylcysteine, USP is synthesized in (b) (4). The particle size of the drug substance is not important because it is a BCS Class I compound with high solubility and high permeability, (b) (4) and the drug product is dissolved in water at the time of administration. The bulk drug substance is stored in (b) (4). (b) (4)-Month retest period for acetylcysteine, USP is proposed and granted.

Acetylcysteine, USP is manufactured and controlled according to the procedures described in DMF (b) (4) from (b) (4) conforms to the requirements (specification) for formulation of acetylcysteine effervescent tablets as described in this NDA.

B. Drug Product [Established Name] Quality Summary

CETYLEV (acetylcysteine) effervescent tablets are indicated for acetaminophen overdose to prevent or lessen hepatic injury.

Acetylcysteine effervescent tablets are supplied in two strengths, 500 mg and 2.5 g. They are white, round, flat tablets with lemon and peppermint flavors. The 500 mg tablets are debossed with "T" on one side and the 2.5 g tablets are debossed with "O" on one side. Each tablet contains 500 mg or 2.5 g of acetylcysteine, USP and the following inactive ingredients: sodium bicarbonate, maltodextrin, lemon flavor, sucralose, peppermint flavor and edetate disodium.

Acetylcysteine effervescent tablets are packaged in 2-count blister packs with one individual tablet in each cavity. The drug product will be supplied in cartons containing 5 blister packs (10 tablets) or 10 blister packs (20 tablets) per carton of 500 mg or 2.5 g tablets.

The drug product manufacturing process involves (b) (4)

Based on the stability data submitted 24-month expiration dating period was proposed and deemed well justified when stored at room temperature in the proposed container closure system, blister packs and cartons.

The drug product manufacturing process proposed by the applicant consisting of the following critical manufacturing process controls to produce consistent quality drug product is deemed adequate.



(b) (4)

The identity, strength, purity and quality of the drug product are assured by the adequate raw material controls, validated manufacturing process, and drug product specification.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	CETYLEV
Non Proprietary Name of the Drug Product	Acetylcysteine
Non Proprietary Name of the Drug Substance	Acetylcysteine
Proposed Indication(s) including Intended Patient Population	An antidote for acetaminophen overdose
Duration of Treatment	3 Days
Maximum Daily Dose	Up to 15 grams every 4 hours
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

A comparative pivotal bioequivalence (BE) study AR 10.001 demonstrated that CETYLEV effervescent tablets are bioequivalent to the reference listed drug, 20% acetylcysteine solution (ANDA 203853).

As CETYLEV effervescent tablets are designed to disintegrate in water prior to oral administration the proposed disintegration test method and acceptance criterion , (b) (4) minutes disintegration (effervescent) time is acceptable.

E. Novel Approaches

N/A

F. Any Special Product Quality Labeling Recommendations

N/A

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)**Application Technical Lead Signature:**

From the quality perspective this NDA is not deemed ready for approval at this time in its present form per 21 CFR 314.125(b)(6) until the label/labeling issues are satisfactorily resolved (see the List of Deficiencies on p. 144).

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
11/09/2015

Hitesh N.
Shroff -S

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DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
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33, cn=Hitesh N. Shroff -S
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Secondary Review Comments and Concurrence:**I concur.****Grace McNally, Branch Chief (acting), OPF/DIA/B3****November 6, 2015****ASSESSMENT OF THE BIOPHARMACEUTICS****BACKGROUND**

The Applicant, Arbor Pharmaceuticals, LLC, submitted this original **NDA 207916** on 03/30/2015 for their proposed drug product, CETYLEV (Acetylcysteine Effervescent Tablets, 500mg and 2.5g), for the indication as an antidote to prevent or lessen hepatic injury [REDACTED] (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen.

This NDA 207916 is a 505(b)(2) application. No safety and efficacy studies were conducted in support of this current application. A comparative pivotal bioequivalence (BE) study AR10.001 was submitted. The purpose of this BE study (AR10.001) was to bridge the proposed product CETYLEV (Acetylcysteine Effervescent Tablets) for oral solution to the reference listed drug (RLD) Mucomyst solution (NDA 13601, approved on 09/14/1963). This pivotal BE study (AR10.001) is titled as “An Open Label, Randomized, Two-Arm, Single-Dose, Two-Period, Crossover Study to Determine the Relative Bioavailability of AR10 (Acetylcysteine Effervescent Tablets for Oral Solution [0.5 g and 2.5 g]) as Compared to Reference Product (Acetylcysteine solution; Oral 20% [200mg/ml]) in Healthy Adult, Human Subjects, Under Fasting Conditions”.

The Division of Biopharmaceutics focuses on reviewing: (1) the pivotal BE study AR10.001, and (2) the disintegration characteristics of the proposed drug product as effervescent tablets.

BIOPHARMACEUTICS ASSESSMENT**1. The composition of proposed drug product**

Two strengths of drug product (Acetylcysteine Effervescent Tablets, 500 mg and 2.5 g) are proposed seeking approval. The composition/formulation is shown below in Table 1 (from M. 2.3.P), which are [REDACTED] (b) (4).

Table 1: Quantitative Composition for Acetylcysteine Effervescent Tablets, 500 mg and 2.5 g

Component	Quality Standard	Function	Amount (mg) per tablet		% w/w (for both tablets)
			500 mg tablet	2.5 g tablet	
Acetylcysteine	USP	API	500.00	2500	54.35%
Sodium bicarbonate	USP	(b) (4)	320.00	1600	34.78%
Maltodextrin	NF	(b) (4)			
Lemon flavor	In-House Standard	(b) (4)			
Sucralose	NF	(b) (4)			
Peppermint flavor	In-House Standard	(b) (4)			
Edetate disodium	USP	(b) (4)			
(b) (4)					
(b) (4)					

Reviewer’s Assessment:
 Both proposed strengths effervescent tablets were used in the pivotal BE study (AR10.001) at a dose level of 11 g (four 2.5 g and two 500 mg tablets) given in 300 mL water, therefore, no biowaiver issue is needed for the proposed two strengths.

2. Disintegration Testing of Drug Product

The drug product is designed to disintegrate in water prior to oral administration. The disintegration (effervescence) time is therefore proposed instead of dissolution time. The disintegration testing was performed according to (b) (4) disintegration method 12101115. The proposed disintegration (effervescence) acceptance limit for drug quality control is NMI^(b)₍₄₎ **minutes** based on (b) (4). The proposed disintegration method and specification are summarized in Table 2 below (from M. 2.3.P), and the detailed disintegration method 12101115 is listed in Appendix 1 (from M. 3.2.P.5)

Table 2: The Proposed Disintegration Method and Specification

Test	Disintegration (effervescence) time
Method Number	12101115

Analytical Conditions and Procedure	<ul style="list-style-type: none"> Purified Water (150 and 300 mL) Temperature between 15 and 25°C When the evolution of gas around the tablet or its fragments ceases the tablet has disintegrated, being either dissolved or dispersed in the water so that no agglomerates of particles remain
Tested Samples	N = 3 per strength of tablets
Specification	NMT ^(b) ₍₄₎ minutes (for both 0.5 and 2.5 g tablets)

The tested batches were manufactured by (b) (4)
(b) (4) (Table 3 below for detailed batch information, from M. 3.2.P.5) and are the same as the to-be-marketed batches.

Table 3: Drug Product Batch Details for Disintegration Testing

Strength: 500 mg						
Batch size: ^(b) ₍₄₎ kg						
Batch No.	028L13		029L13		030L13	
Purpose	Registration/Stability		Registration/Stability		Registration/Stability/Clinical	
	A	B	A	B	A	B
Manufacturing Date	27Nov 2013	27Nov 2013	27Nov 2013	27Nov 2013	28Nov2013	28Nov2013
Drug Substance Lot	0023-3	0023-3	0017-3	0017-3	0023-3 (^(b) ₍₄₎ kg)	0023-3 (^(b) ₍₄₎ kg)
Disintegration (effervescence) time	(b) (4)					
Disintegration (effervescence) Specification	NMT ^(b) ₍₄₎ minutes					
Strength: 2.5 g						
Batch size: ^(b) ₍₄₎ kg						
Batch No.	031L13		032L13		033L13	
Purpose	Registration/Stability		Registration/Stability		Registration/Stability/Clinical	
	A	B	A	B	A	B
Manufacturing Date	29Nov 2013	29Nov 2013	29Nov 2013	29Nov 2013	29Nov 2013	29Nov 2013
Drug Substance Lot	0023-3	0023-3	0023-3	0023-3	0023-3 (^(b) ₍₄₎ kg)	0023-3 (^(b) ₍₄₎ kg)
Disintegration (effervescence) time (seconds)	(b) (4)					
Disintegration (effervescence) Specification	NMT ^(b) ₍₄₎ minutes					

The disintegration testing also measured the lowest dose of Acetylcysteine (2 g in 150 mL water (b) (4), and ^(b)₍₄₎g in 300 mL water (b) (4)), and the

highest dose of Acetylcysteine ((b) (4) g in 150 mL water (b) (4) and 15 g in 300 mL water (b) (4)).

In original submission, the Applicant provided individual disintegration testing data on the lowest dose (2 g) and the highest dose ((b) (4) g) of Acetylcysteine in 150 mL water (b) (4) (from M. 2.7.1). In the Biopharmaceutics Information Request (sent on 08/06/2015), the Agency requested for individual disintegration testing data on lowest dose ((b) (4) g) and the highest dose (15 g) of Acetylcysteine in 300 mL water (b) (4) (b) (4). The Applicant provided the responses on 08/14/2015, including the detailed disintegration data, which is summarized in the following Table 4 (from M. 2.7.1 and IR response dated 08/14/2015, details see Appendix 2).

Table 4: Mean disintegration (effervescence) time on the lowest and highest doses of Acetylcysteine

Acetylcysteine to be administered	Volume of water to be administered to patients	Average Disintegration Time
2 g (lowest dose)	150 mL (b) (4)	(b) (4)
(b) (4) g (highest dose)	150 mL	(b) (4)
(b) (4) g (lowest dose)	300 mL	(b) (4)
15 g (highest dose)	300 mL	(b) (4)

Reviewer’s Assessment:

The disintegration time of proposed effervescence tablets met the proposed specification for NMT (b) (4) minutes. The proposed disintegration time specification of NMT (b) (4) minutes is acceptable. Because of effervescent nature of the tablet, it is acceptable that the product does not need to have a dissolution time specification.

3. Pivotal Bioequivalence (BE) Study (AR10.001)

(1) The regulatory history of using ADNA 203853 as reference drug for BE study in this NDA 207916 submission

Because this NDA 207916 is a 505(b)(2) application, the original listed drug being relied upon is NDA 013601 Mucomyst Oral Inhalation Solution 10% and 20% (Apothecon, approved on 09/14/1963), which has been discontinued from marketing.

The ANDAs being designated as the RLDs in the Orange Book are:

- ANDA 72489 acetylcysteine inhalation solution 10% (Luitpold, approved on 07/28/1995)
- ANDA 72547 acetylcysteine inhalation solution 20% (Luitpold, approved on 07/28/1995) – drug shortage

Other ANDAs not being designated as RLD's in the Orange Book involved in this NDA are:

- ANDA 203853 acetylcysteine inhalation solution 20% (Innopharmaa, approved on 06/21/2012)
- ANDA 72324 acetylcysteine inhalation solution 20% (Roxane, approved on 04/30/1992) – discontinued

In the 01/29/13 pre-IND 116902 meeting, the Applicant asked if [REDACTED] (b) (4) to be relied could be [REDACTED] (b) (4). FDA advised the Applicant that 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, they will need to identify the NDA product (i.e., Mucomyst) that was the basis for submission of the ANDA [REDACTED] (b) (4).

The Applicant also asked if it was acceptable to use Roxane's ANDA 72324 (20%), a non-RLD, in their comparison testing [REDACTED] (b) (4).

[REDACTED] FDA agreed.

When this NDA 207916 was submitted, it was discovered that while the Applicant was able to use Roxane's ANDA 72324 (20%), non-RLD, for the physical and chemical testing, the Applicant used Innopharmaa's ANDA 203853 (20%), another non-RLD, in their BE study. Roxane's ANDA 72324 (20%) became unavailable (Roxane's ANDA 72324 is now listed as discontinued in the Orange Book). The Applicant explained that [REDACTED] (b) (4) they chose Innopharmaa's ANDA 203853 (20%), non-RLD, in alignment with FDA's previous advice about using Roxane's ANDA 72324 (20%), non-RLD, [REDACTED] (b) (4).

The review team found it is acceptable from a scientific perspective that the Applicant's use of Roxane's ANDA 72324 (20%) in the physical/chemical testing and Innopharmaa's ANDA 203853 (20%) in the BE study. In addition, from a regulatory perspective, the Applicant's explanation [REDACTED] (b) (4) is also acceptable. Therefore, Innopharmaa's ANDA 203853 (20%) is acceptable in the BE study for this NDA 207916 application. (Agency's IR on 05/29/2015, Applicant's response on 06/10/2015, 505(b)(2) issue generated on 06/17/2015, decision email dated on 06/30/2015) (see [Appendix 3](#) for details).

It is noted that Innopharma's ANDA 203853 (20%) was granted for waiver of bioequivalence testing compared to the RLD Luitpold's ANDA 72547 (20%) by the

Division of Bioequivalence II (DB II) based on the biowaiver per Section 21 CFR 320.22(b)(3) (submitted on 01/06/2012, approved on 03/19/2012) (Biowaiver granted letter in [Appendix 4](#) for details).

Reviewer's Assessment:

Based on the decision made by the Agency earlier, ANDA 203853 (20% acetylcysteine solution) is acceptable as reference drug in the submitted BE study (AR10.001) for this NDA 207916 (acetylcysteine effervescence tablets).

(2) BE Study Design Features

Title of Study: An Open Label, Randomized, Two-Arm, Single-Dose, Two-Period, Crossover Study to Determine the Relative Bioavailability of AR10 (Acetylcysteine Effervescent Tablets for Oral Solution [0.5 g and 2.5 g]) as Compared to Reference Product (Innopharma's Acetylcysteine solution; Oral 20% [200mg/ml]) in Healthy Adult, Human Subjects, Under Fasting Conditions.

Objectives: To assess the relative bioavailability of a single dose level of 11 g of test product (AR10, acetylcysteine effervescent tablets for oral solution [two 0.5 g and four 2.5 g tablets]), and 11 g of the reference product (acetylcysteine solution; oral 20% [55 mL of 200 mg/mL]) in healthy adult, human subjects under fasting conditions.

Dosage Rationale, Duration of Treatment: Dosage size for each acetylcysteine product is based on the to-be treated patient's weight. In order to standardize the dose for purposes of this study in healthy adults, the dose for a 70 kg patient was selected for all subjects. Subjects received a single dose of study drug at each of two dosing periods for a total of 2 days of treatment. The duration of subject participation in the study was up to approximately 42 days, including an up to 30-day screening period, a 10-day treatment period (including two dosing visits), and a 2-day follow-up period. A wash-out period of 7 days was employed.

Test Product, Dose and Mode of Administration, Lot Number: The test product AR10, acetylcysteine effervescent tablets, used were 0.5 g (Lot number 030L13) and 2.5 g (Lot number 033L13), expiration date: 29 November 2014 (details in [Table 5](#) below, from M. 5.3.1).

After an overnight fasting for at least 10 hours, subjects were orally administered a solution of 11 g (four 2.5 g and two 0.5 g tablets) of AR10 effervescent tablets in 300 mL water. After the complete dose was consumed, the dosing glass was rinsed with 100 mL of water and the water was swallowed.

Reference Therapy, Dose and Mode of Administration, Lot Number: The reference product is acetylcysteine 20% inhalation solution (200 mg/mL, Lot number SG362, Expiration date: June 2015, details in [Table 5](#) below, from M. 5.3.1). After an overnight fasting for at least 10 hours, subjects were orally administered 55 mL of 20%

acetylcysteine solution (total of 11 g acetylcysteine) diluted with 165 mL of diet caffeine-free soft drink. After consuming this, 80 mL of room temperature water were poured into the same container and swallowed, for a total volume of 300 mL (equal to the test product oral volume intake). After the complete dose was consumed, the dosing glass was rinsed with 100 mL of water and the water was swallowed.

Table 5: Test and Reference Drug Product Formulations

Drug Information	AR10 Test Formulation	Reference Formulation
Generic Name	Acetylcysteine	Acetylcysteine
Strength	0.5 g and 2.5 g	20% (200 mg/mL)
Formulation	Effervescent Tablets	Inhalation Solution (Not for Injection)
Source of Supply	Alpex Pharma SA Via Cantonale 6805 Mezzovico (Lugano) Switzerland for Arbor Pharmaceuticals, LLC	Manufactured by Gland Pharma Limited, INDIA for APP Pharmaceuticals, LLC Schaumburg, Illinois 60173
Lot Number	0.5 g: Lot number 030L13 2.5 g: Lot number 033L13 Expiration date: (b) (4)	Lot number: SG362 Expiration date: June 2015

Disposition/Demographics Results: Thirty healthy subjects (15 subjects per treatment group) were enrolled, randomized and received study treatment. All 15 subjects in T1T2 completed Period 1 and Period 2 of the study. In T2T1, all 15 subjects completed Period 1, and 14 of 15 subjects completed Period 2 of the study. Twenty-nine of 30 subjects completed both periods of the study as planned, comprising the PK population. One subject (#119) in T2T1 discontinued the study during Period 2 due to adverse events (AEs) of syncope and seizure-like activity (Preferred Term [PT]: convulsion) that occurred prior to test drug AR10 administration. This subject was withdrawn from the study the following day. Mean (SD) age of subjectss was 35.2 (9.14) years, and race, in descending order was 18 (60%) White and 12 (40%) Black/African American. Demographic and other baseline characteristics were similar between the T1T2 and T2T1 groups.

Reviewer’s Assessment:

The proposed BE study design is acceptable.

(3) Bioanalytical Analysis

Drug Concentration Measurements: Serial blood samples were collected from all subjects on Day 1 and Day 8 for the measurement of total acetylcysteine in human plasma. Samples for pharmacokinetics (PK) analysis were collected at pre-dose and at 15, 30, 45 minutes and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36, and 48 hours post-dose in each period. The pre-dose sample was obtained within 60 minutes prior to dosing.

Endogenous Total Acetylcysteine Baseline Justification: Plasma samples of all subjects were assayed for acetylcysteine using bioanalytical methods that were developed and validated according to the Sponsor/designee SOPs in order to quantify the total acetylcysteine in human plasma (Bioanalytical Method BAM.0194.02, from M. 5.3.1, Sample Analysis Report # 0132-1281, and M. 5.3.1, Validation Report # 0132-1280, and M. 5.3.1, Validation Report Amendment # 0132-1280).

Since acetylcysteine is known to be endogenous in human plasma (discussed in PIND 116902 meeting), several lots of plasma were screened by the Applicant in order to find the lowest background level of total acetylcysteine. The raw response and calculated results are provided in the following Table 6. The representative chromatography is showed in Figure 1 below. The results indicated that the amount of total acetylcysteine observed in various unspiked plasma pools ranged from ~20-70% of the lower limit of quantification (LLOQ).

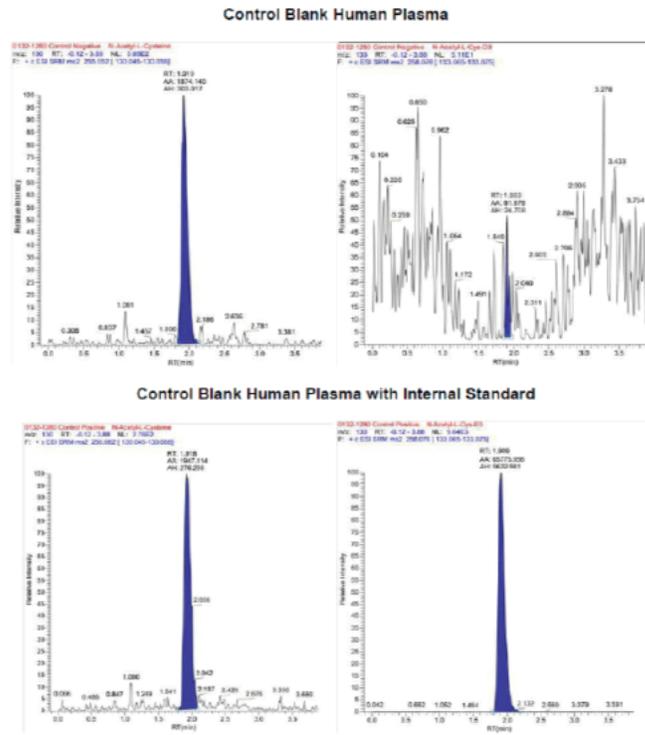
The endogenous level of total acetylcysteine in human plasma was detected at least ~20% of LLOQ, while all plasma samples post dosing have at least 2.5-fold higher concentration of total acetylcysteine than the LLOQ.

Table 6: The raw response and calculated results from acetylcysteine chromatography

Run ID	Sample Type	Sample Name	Analyte Area	Analyte Area / (Analyte Mean LLOQ)	ISTD Area	ISTD Area / (ISTD Mean LLOQ)
8	Blank Matrix Lots	LOT A	6094	70.3%	36	0.1%
		LOT B	1917	22.1%	95	0.1%
		LOT C	2133	24.6%	45	0.1%
		LOT D	2561	29.6%	23	0.0%
		LOT E ^b	3156	36.4%	82	0.1%
		LOT F ^c	1681	19.4%	15	0.0%
	LLOQ 1 & 2	LLOQ 1	8963		66547	
		LLOQ 2	8365		62971	
	Mean LLOQ		8664		64759	

Figure 1: Sample Chromatograms – Run 8

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Reviewer’s Assessment:

The background (endogenous) concentration of total acetylcysteine is considered to have minimally significant impact on the study results. Therefore, as previously agreed upon between the Applicant and the Agency, the acetylcysteine baseline does not need to be justified (corrected) for the PK data analysis.

(4) BE Study Results

Plasma Concentration: Plasma samples were assayed for total acetylcysteine using validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) procedures by the Applicant. Total acetylcysteine concentration-vs-time profiles, showing mean (±SD) concentration values for the PK population, are presented in linear and semilog scales in the following Figure 2 and 3 (from M. 5.3.1.2).

Figure 2: Mean (\pm SD) Concentrations of Total Acetylcysteine – Linear Scale (PK Population)

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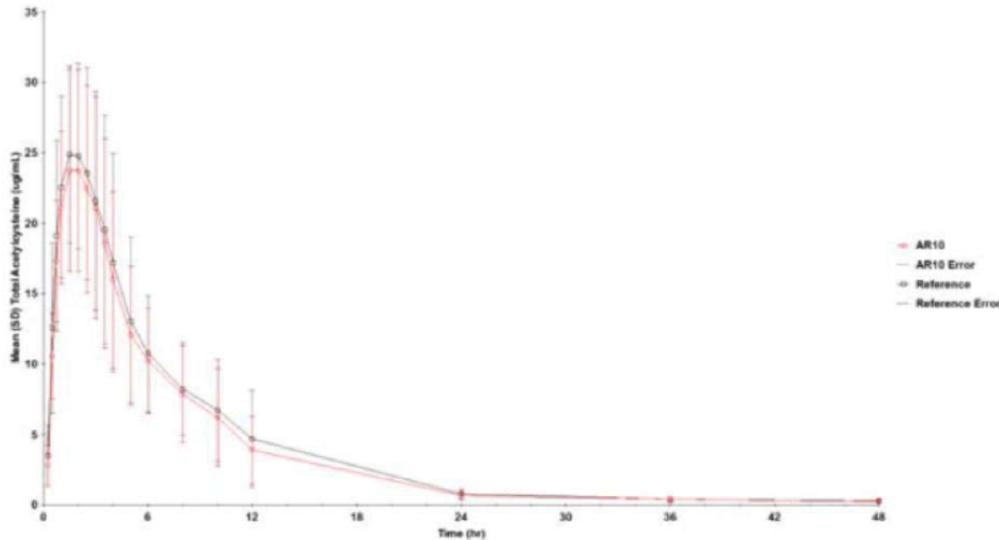
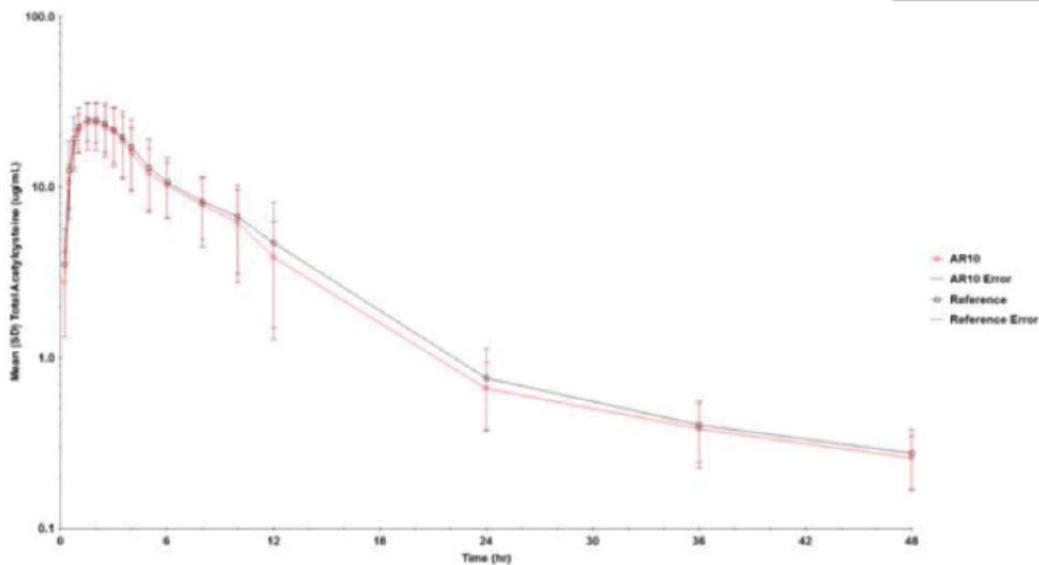


Figure 3: Mean (\pm SD) Concentrations of Total Acetylcysteine – Semilog Scale (PK Population)

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PK Analysis and Parameters: Concentration-time data for total acetylcysteine for individual subjects were analyzed by the Applicant using non-compartmental methods in WinNonlin[®] version 5.3. Summary statistics for the total acetylcysteine mean PK parameters are listed in Table 7 below (from M. 5.3.1.2).

Table 7: Summary Statistics: Total Acetylcysteine Mean PK parameters

Treatment		Tlag (hr)	Cmax (ug/mL)	Tmax (hr)	AUClast (hr*ug/mL)	AUCinf (hr*ug/mL)	AUCextrap (%)	λz (1/hr)	t1/2 (hr)	CL/F (L/hr)	Vz/F (L)	Fr (%)
AR10	N	29	29	29	29	29	29	29	29	29	29	29
	Mean	0.00	26.5	2.12	179	186	3.61	0.0404	18.1	65.1	1720	94.0
	SD	0.00	7.58	0.677	52.3	54.3	0.939	0.0112	3.96	22.8	731	18.5
	Min	0.00	14.6	1.00	76.8	80.3	1.48	0.0273	8.09	35.6	647	52.2
	Median	0.00	24.6	2.00	179	185	3.48	0.0396	17.5	59.3	1600	96.3
	Max	0.00	42.5	3.50	298	309	5.73	0.0857	25.4	137	3680	126
	CV%		28.6	31.9	29.2	29.2	26.0	27.6	21.9	35.0	42.6	19.7
Reference	N	29	29	29	29	29	29	29	29	29	29	29
	Mean	0.00	28.4	1.89	195	202	3.43	0.0407	17.5	59.3	1510	
	SD	0.00	7.86	0.800	62.6	64.4	0.842	0.00703	2.98	16.3	503	
	Min	0.00	16.7	0.500	120	124	2.10	0.0275	12.3	28.8	664	
	Median	0.00	26.2	1.50	177	185	3.37	0.0397	17.4	59.6	1600	
	Max	0.00	47.6	4.00	370	382	5.69	0.0563	25.2	89.1	2470	
	CV%		27.6	42.4	32.1	32.0	24.5	17.3	17.0	27.4	33.2	

CV = coefficient of variation; max = maximum; min = minimum; PK = pharmacokinetic; SD = standard deviation

BE Analysis and Results: BE results of the test and the reference products with respect to C_{max}, AUC_{last}, and AUC_{inf} are listed in Table 8 below (from M. 5.3.2.1). The mean relative bioavailability and the 90% confidence interval (CI) were calculated as 92.64% (86.84%–98.84%) for C_{max}, 92.11% (86.18%–98.44%) for AUC_{last}, and 92.28% (86.39%–98.56%) for AUC_{inf}.

Table 8: Total Acetylcysteine Bioequivalence Confidence Intervals (PK Population)

Test	Reference	Parameter	Units	Ref LSM	AR10 LSM	Ratio [% Ref]	90% CI		ANOVA CV%
							Lower Bound	Upper Bound	
AR10	Reference	AUC _{inf}	h*ug/mL	192.15	177.31	92.28	86.39	98.56	14.81
		AUC _{last}	h*ug/mL	185.54	170.90	92.11	86.18	98.44	14.94
		C _{max}	ug/mL	27.46	25.44	92.64	86.84	98.84	14.54

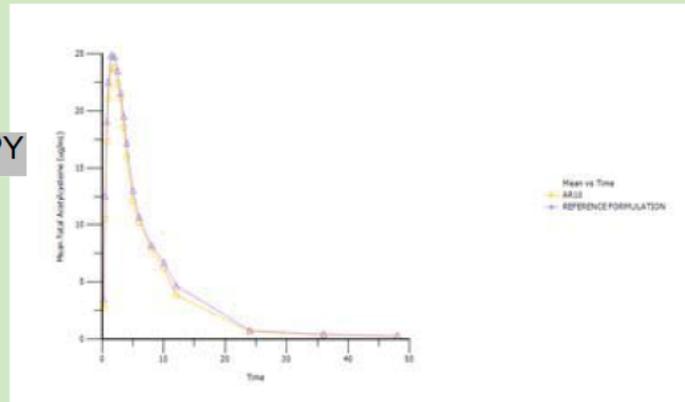
ANOVA = analysis of variance; CI = confidence interval; CV = coefficient of variation; LSM = least squares means; Ln = natural logarithm; LSM = least square mean; PK = pharmacokinetic; Ref = reference

The median difference in T_{max} values between the test and the reference product was small (0.50 hr).

Reviewer’s Assessment:

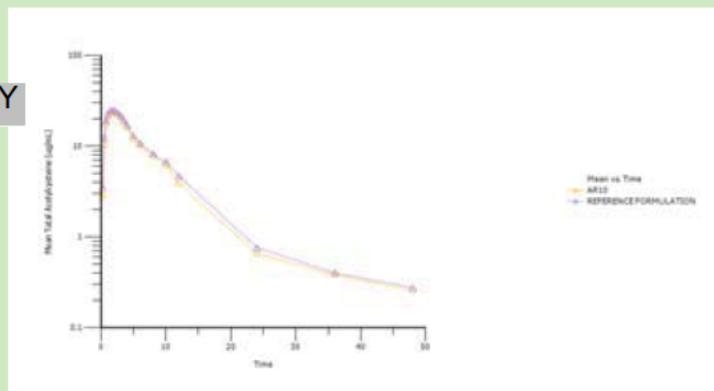
By using the provided Pharmacokinetic Concentrations Dataset (pc.xpt) (Study AR10.001, ADPP – Pharmacokinetics Parameter Analysis – Analysis Dataset, from M. 5.3.1.2), this reviewer verified: (1) the similar total acetylcysteine concentration-vs-time profiles in linear and semilog scales (Figure 4 and 5 below); (2) the similar PK parameters, relative bioavailability and 90% CI results using WinNonLin version 6.4, which are all comparable with the submitted PK profiles and BE data (Table 9 below). Therefore, the proposed drug and the reference drug are concluded to be “bioequivalent”.

Figure 4: Mean (\pm SD) Concentrations of Total Acetylcysteine – Linear Scale (PK Population) (By This Reviewer)



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Figure 5: Mean (\pm SD) Concentrations of Total Acetylcysteine – Semilog Scale (PK Population) (By This Reviewer)



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Table 9: Total Acetylcysteine Bioequivalence Confidence Intervals

In NDA Submission

Test	Reference	PK Parameters	Units	T/R Ratio	90% CI Lower	90% CI Upper
AR10	Reference	AUC _{inf}	h*ug/mL	92.28	86.39	98.56
		AUC _{last}	h*ug/mL	92.11	86.18	98.44
		C _{max}	ug/mL	92.64	86.84	98.94

By This Reviewer

Test	Reference	PK Parameters	Units	T/R Ratio	90% CI Lower	90% CI Upper
AR10	Reference	AUC _{inf}	h*ug/mL	92.29	86.27	98.73
		AUC _{last}	h*ug/mL	91.89	85.77	98.45
		C _{max}	ug/mL	92.70	86.98	98.79

4. Biopharmaceutics Inspection

The Applicant provided the information of clinical site and bioanalytical laboratory for the submitted BE study (AR10.001) performance, which are listed in the following Table 10 (from M. 5.3.1).

Table 10: The listed organization involved in the conduct of BE study (AR10.001)

Role	Organization, Contact Information
Clinical trial oversight and approvals, management of decision escalation and medical issues	Sponsor: Arbor Pharmaceuticals, LLC Six Concourse Parkway, Suite 1800 Atlanta, GA 30328
Clinical site, unblinded study drug dispensing and accountability, PK sample management, data management	Spaulding Clinical 525 S. Silverbrook Drive West Bend, Wisconsin 53095
Project management, safety surveillance, data management, biostatistics, clinical monitoring, safety monitoring, clinical study report preparation	(b) (4)
Clinical laboratory	
Pharmacokinetic analysis	
Bioanalysis management	
Bioanalytical laboratory	

On 05/19/2015, the Division of Biopharmaceutics requested the Office of Study Integrity and Surveillance (OSIS) for the Biopharmaceutical Inspections on both the Clinical Site (Spaulding Clinical) and the Bioanalytical Site ((b) (4)) (see Appendix 5 for details). On 07/01/2015, the OSIS recommended to accept data without an on-site inspection for the Clinical Site (Spaulding Clinical, 525 S. Silverbrook Drive, West Bend, WI 53095) (see Appendix 6 for details). On 08/31/2015, the OSIS recommended that the analytical data from study AR10.001 be accepted for further Agency review, after inspecting the Bioanalytical Site ((b) (4)) (see Appendix 7 for details).

Reviewer's Assessment:

The Biopharmaceutics Inspections on both the Clinical Site (Spaulding Clinical) and the Bioanalytical Site ((b) (4)) are considered acceptable; therefore, the above bioanalytical data of plasma total acetylcysteine for PK analysis and BE calculation is acceptable for review.

5. Labeling Section 12.3 (Pharmacokinetics)

On 09/25/2015, the Agency sent one labeling Information Request (IR) to the Applicant to revise Labeling Section 12.3 (Pharmacokinetics) to align with the Clinical Pharmacology draft labeling guidance, as following:

Section 12.3 (Pharmacokinetics) in the Prescribing Information currently contains information on (b) (4)

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.

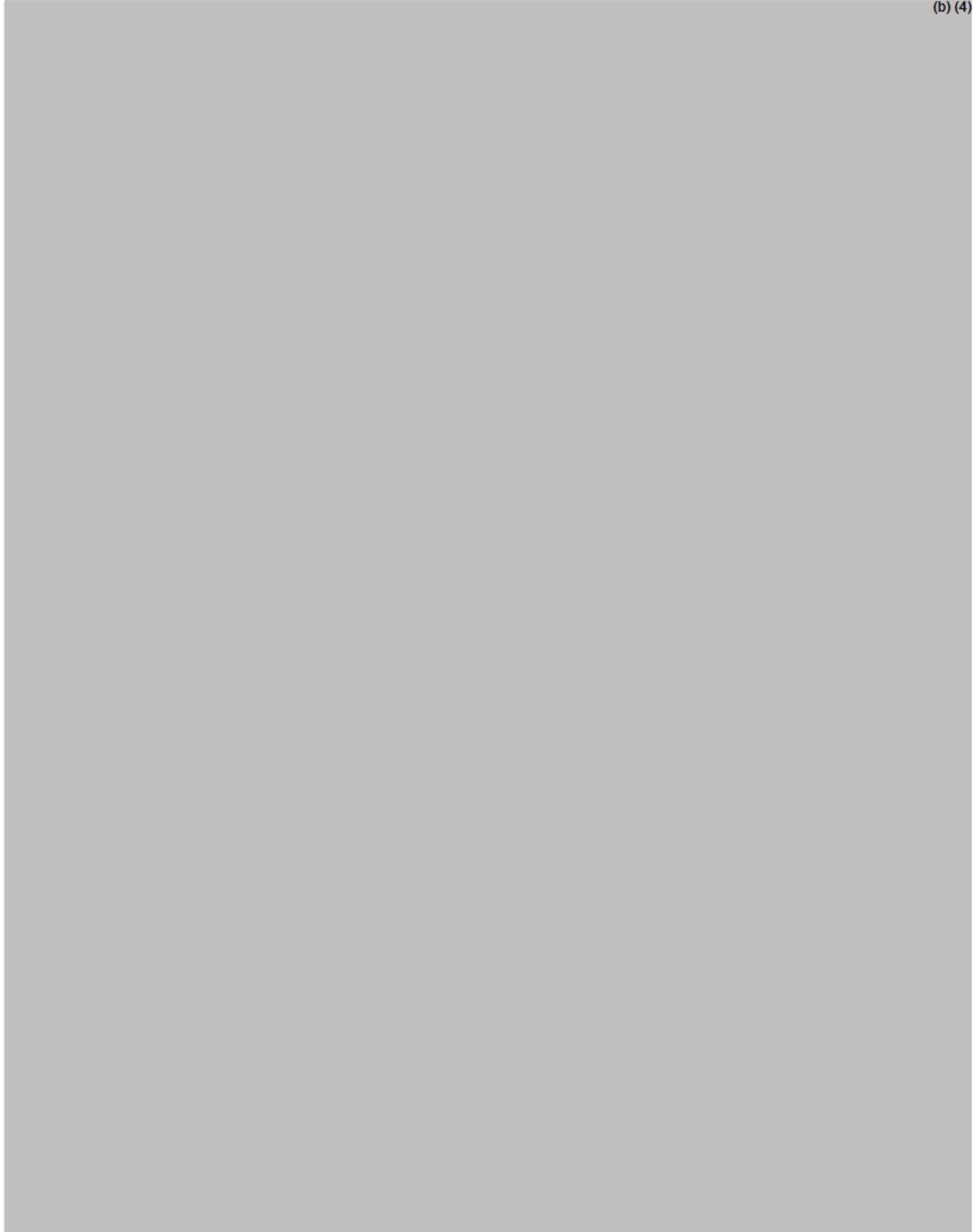
On 10/06/2015, the Applicant provided the response to this IR, revised the labeling section 12.3 (pharmacokinetics) using the pharmacokinetic information obtained from dosing healthy subjects with Cetylev tablets in the BE study AR10.001, as well as literature search to obtain any additional knowledge regarding ADME of acetylcysteine in humans (see Appendix 8 for detailed revised labeling section 12.3 provided by the Applicant).

Reviewer's Assessment:

This reviewer has confirmed that the stated mean pharmacokinetic parameters, C_{max} , AUC_s , and plasma half-life ($T_{1/2}$) are obtained from the BE study AR10.001, therefore, they are acceptable without further revisions. The rest of the labeling section 12.3 (pharmacokinetics) is currently under review by other disciplines.

Appendix 1

(b) (4) **disintegration method 12101115 (from M.3.2.P.5.2)**



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Appendix 2

Disintegration Testing Results:

(1) The individual disintegration testing data on the lowest dose of Acetylcysteine (2 g) and the highest dose of Acetylcysteine (^(b)₍₄₎ g) in 150 mL water ^(b)₍₄₎ (from M. 2.7.1).

NAC to be administered (g)	Number of Eff. tablets containing 2.5 g of NAC to be administered (batch 033L13(A))	Number of Eff. tablets containing 0.5 g of NAC to be administered (batch 030L13(A))	Trial #	Disintegration Time (sec)	Average Disintegration Time (sec)	Volume of reconstituted solution to be administered to patients
^(b) ₍₄₎						

(2) The individual disintegration testing data on lowest dose of Acetylcysteine (^(b)₍₄₎g) and the highest dose of Acetylcysteine (15 g) in 300 mL water ^(b)₍₄₎ (Information Request dated on 08/06/2015, response dated on 08/14/2015).

Biopharmaceutics Information Request: 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.

Response: Detailed batch information for product used for disintegration testing as described in 2.3.P.2, along with results, is provided in Table 1. Disintegration testing was performed on the lowest dose ((b) (4)g NAC in 300 mL water) and the highest dose (15 g NAC in 300 mL water) to represent the potential dosing schedule as presented in the currently approved dosing table of the Reference Listed Drug. The test was performed with water at a temperature of 15-25°C.

Table 1: Disintegration Testing in 300 mL Water (Lowest and Highest Dosing)

Batch Number	Manufacturing Date	Proposed Expiration Date	Disintegration Testing Date	Individual Disintegration Results (seconds)	Average Disintegration Result (seconds)
030L13 (500 mg)	28Nov2013	28Nov2015	05Aug2014	(b) (4)	(b) (4)
033L13 (2.5 g)	29Nov2013	29Nov2015	05Aug2014		

Appendix 3

The documents of regulatory history of using ADNA 203853 as reference drug for BE study in this NDA 207916 submission

(1) Agency's Information Request dated on 05/29/2015

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 Innopharmaa (b) (4) for your bridging study.

(2) The Applicant's response for above IR dated on 06/10/2015

Arbor's Response: Since Mucomyst solution was discontinued in 2009 and was unavailable, (b) (4), the Agency agreed (FDA minutes dated 27Feb2013, page 4, PIND 116902) that an AN rated acetylcysteine solution product (therapeutic equivalent code for solutions and powders for aerosolization) could be used as the marketed equivalent of the RLD in AR10.001 (ANDA 72-324; Bedford Laboratories, manufactured for Roxane Laboratories, Inc.). (b) (4)

Therefore, in alignment with FDA feedback, another 20% AN rated therapeutic equivalent was selected as the reference product (FDA-approved Innopharmaa, ANDA 203853) and used in AR10.001. Please refer to section 2.5 for further discussion on use of the selected comparator.

(3) 505(b)(2) issue was generated on 06/17/2015, decision was emailed dated on 06/30/2015.

505b2 Issue Number: 56

ADRA Completing Form: Maria Walsh

Date Issue Generated: 6/17/15

Date Response Needed: PDUFA date 1/30/16

Brief Discussion History: (if previously discussed, etc)

Key Words: non-RLD ANDA

Application Number: NDA 207916

Sponsor/Applicant: Arbor Pharmaceuticals

PDUFA Goal/Action Goal Date, if applicable: 1/30/16

Proposed Drug Name: Acetylcysteine

Dosage Form: Effervescent Tablets

Strength(s): 500 mg and 2.5 grams

Proposed Indication(s):

- An antidote to prevent or lessen hepatic injury [REDACTED] (b) (4)
[REDACTED] ingestion of a potentially hepatotoxic quantity of acetaminophen.

Reliance on listed drug(s): include dosage form(s), strength(s), NDA number(s), and sponsor(s) of listed drug(s) relied upon. Indicate if any are discontinued from marketing:

- NDA 013601 Mucomyst Oral Inhalation Solution 10% and 20% (Apothecon) – discontinued from marketing

Reliance on other sources of information, e.g., published literature/final OTC monograph/DESI (pick all that apply, if any): N/A

Describe how the proposed 505(b)(2) product differs from the relied-upon listed drug(s):

Different dosage form

Background: The relied upon listed drug, NDA 013601 Mucomyst Oral Inhalation Solution 10% and 20%, is discontinued.

The ANDAs designated as the RLDs in the Orange Book are:

- ANDA 72489 acetylcysteine inhalation solution 10% (Luitpold)
- ANDA 72547 acetylcysteine inhalation solution 20% (Luitpold) – drug shortage

Other ANDAs not designated as RLD's in the Orange Book involved in this issue are:

- ANDA 203853 acetylcysteine inhalation solution 20% (Innopharma)
- ANDA 72324 acetylcysteine inhalation solution 20% (Roxane) - discontinued

In the 1/29/13 pre-IND meeting, Arbor asked if (b) (4) on which to rely is (b) (4). FDA advised Arbor that while it is appropriate to use the ANDA product (b) (4) in the Orange Book as the comparator in bridging studies when the innovator product has been discontinued, they will need to identify the NDA product (i.e., Mucomyst) that was the basis for submission of the ANDA (b) (4).

Arbor also asked if it was acceptable to use Roxane's ANDA 72324 (20%), a non-RLD, in their comparison testing (b) (4). FDA agreed.

When the NDA was submitted, it was discovered that while Arbor was able to use Roxane's ANDA 72324 (20%), non-RLD, for the physical and chemical testing, Arbor used Innopharma's ANDA 203853 (20%), another non-RLD, in their BE study, when Roxane's ANDA 72324 (20%) became unavailable (Roxane's ANDA 72324 is now listed as discontinued in the Orange Book). Arbor explained that (b) (4) they chose Innopharma's ANDA 203853 (20%), non-RLD, in alignment with FDA's previous advice about using Roxane's ANDA 72324 (20%), non-RLD, (b) (4).

Arbor's full explanation is attached below. The review team finds Arbor's use of Roxane's ANDA 72324 in the physical/chemical testing and Innopharma's ANDA 203853 in the BE study acceptable from a scientific perspective.



Response to
Billing Communi...

Specific issues/questions for discussion:

- From a regulatory perspective, is Arbor's explanation (b) (4) acceptable?

Outcome:

The applicant's rationale was acceptable from a regulatory perspective.

Appendix 4

Innopharma’s ANDA 203853 (20%) was granted for waiver of bioequivalence testing compared to the RLD Luitpold’s ANDA 72547 (20%) by the Division of Bioequivalence II (DB II) based on the Section 21 CFR 320.22(b)(3) (submitted on 01/06/2012, approved on 03/19/2012).

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	203853
Drug Product Name	Acetylcysteine Solution, USP
Strength(s)	20%
Applicant Name	InnoPharma, Inc.
Address	10 Knightsbridge Road, N/A Piscataway, NJ 08854
Applicant’s Point of Contact	Christy Meng
Contact’s Telephone Number	732.885.2939 (ext. 116)
Contact’s Fax Number	732.885.1248
Original Submission Date(s)	January 6, 2012
Submission Date(s) of Amendment(s) Under Review	N/A
Reviewer	Jennifer N. Miller, Ph.D.
OUTCOME DECISION	ADEQUATE

1 EXECUTIVE SUMMARY

The firm, InnoPharma, Inc. has requested a waiver of *in vivo* bioequivalence requirements based on 21 CFR § 320.22 (b) (3) for its Acetylcysteine Solution, USP, 20%. The RLD is Acetylcysteine Solution, 20%, manufactured by Luitpold.

Based on the information submitted, the test product contains the same amount of the active ingredient as the reference listed drug and all of the inactive ingredients of the test product are within the IIG limits. Based on the information provided, the DB II grants InnoPharma, Inc. the waiver request for *in vivo* BE study requirements for Acetylcysteine Solution, USP, 20%, based on criteria set forth in Section 21 CFR § 320.22 (b) (3).

The application is **adequate**.

2 TABLE OF CONTENTS

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Acetylcysteine Solution, USP, 20%
Reference Product	Acetylcysteine Solution, 20%
RLD Manufacturer	Luitpold
NDA No.	072547
RLD Approval Date	July 28, 1995
Indication	Acetylcysteine is indicated as adjuvant therapy for patients with abnormal, viscid, or inspissated mucous secretions.

3.2 PK/PD Information

Bioavailability	Acetylcysteine is administered orally, intravenously, or via inhalation. After oral inhalation, the majority of the administered dose undergoes a sulfhydryl-disulfide reaction; only a small portion of the dose is absorbed from the pulmonary epithelium.
Food Effect	N/A
T _{max}	N/A
Metabolism & Excretion	Most of an acetylcysteine dose is expected to be metabolized and incorporated as cysteine into cellular pools. After 24 hours, 22% of a radioactive dose of S-acetylcysteine is excreted in the urine. No metabolites have been identified in the urine.
Half-life	5.6 hours
Drug Specific Issues (if any)	N/A
Dosage & administration	<p><u>Inhalation Administration</u></p> <ul style="list-style-type: none"> Solutions for inhalation are not FDA approved for parenteral injection. The 20% solution may be administered undiluted or, if desired, may be diluted in sterile NS injection, sodium chloride for inhalation, or sterile water for injection or inhalation. Acetylcysteine reacts with certain materials (e.g., iron, nickel, copper, rubber); therefore, any part of the nebulizer equipment that comes in contact with acetylcysteine should be made of plastic or glass. <p><u>Nebulization Inhalation Administration</u></p> <ul style="list-style-type: none"> Ultrasonic or conventional nebulizers may be used. Hand-bulb nebulizers produce particles which are too large and the output is usually too small. Compressed air should be used to provide pressure. Administer nebulizer solution directly or using a plastic face mask, face tent, mouthpiece, oxygen tent, or head tent. The nebulizer may also be fitted into intermittent positive pressure breathing (IPPB) machines. During administration, after ¾ of the initial volume has been nebulized, dilute the remaining solution with an equal amount of NS or sterile water. Immediately after administration, clean nebulizing equipment to prevent occlusion of fine orifices or corrosion of metal parts.

3.3 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	Yes	1
BCS Waivers	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

3.4 Formulation

Formulation of Test Product: Acetylcysteine Solution, USP, 20%

INGREDIENTS	GRADE	FUNCTION	QUANTITY PER ML	QUANTITY/ UNIT
Acetylcysteine*	USP	Active Ingredient	200 mg	6.00 g
Disodium Edetate	USP	(b) (4)	0.5 mg	15.0 mg
Sodium Hydroxide	NF	Alkalizing agent	q.s for pH adjustment	q.s for pH adjustment
Hydrochloric Acid**	NF	Acidifying agent	q.s for pH adjustment	q.s for pH adjustment
Water for Injection	USP	(b) (4)		(b) (4)

* Theoretical quantity of acetylcysteine is calculated based on as is basis.

**Hydrochloric Acid is added only if it is need to adjust the pH. (b) (4)

(b) (4)

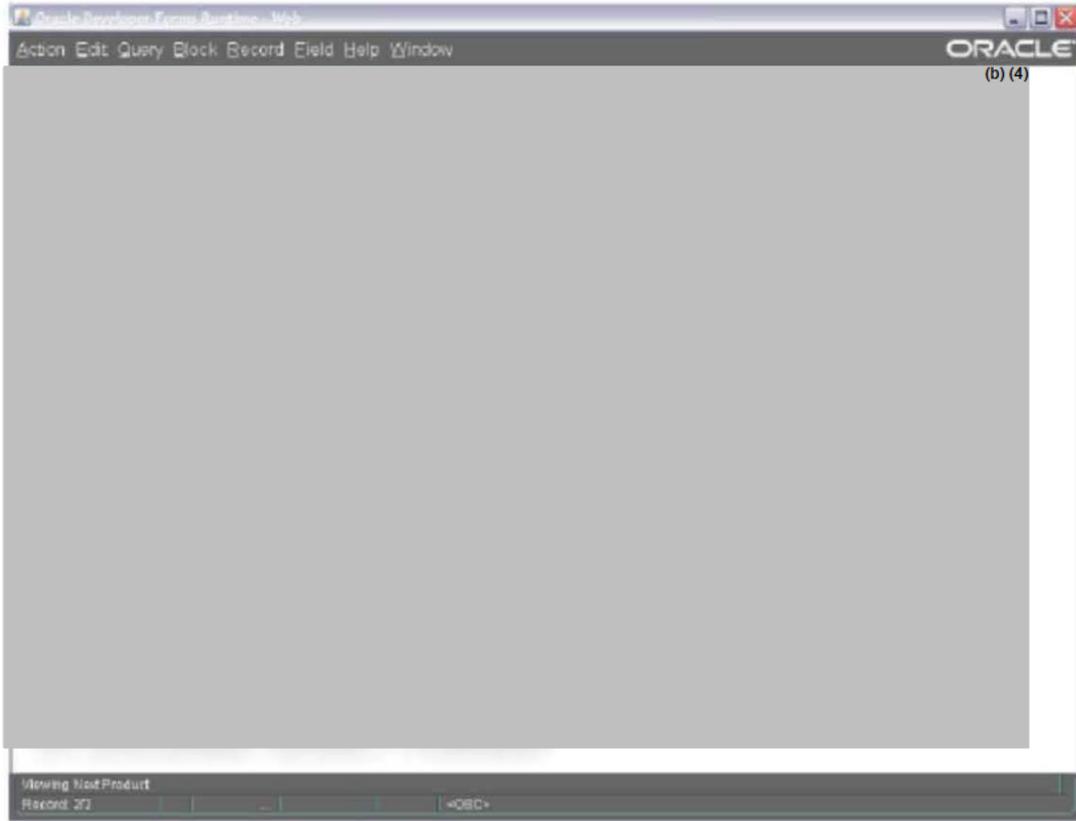
q.s = quantity sufficient

**Formulation Comparison with Reference Listed Drug: ANDA 072547
Acetylcysteine Solution, 20% (Luitpold)**

Components	RLD, Luitpold's Acetylcysteine Solution USP 20%		InnoPharma's Acetylcysteine Solution USP 20%	
	(mg/mL)	% (w/v)	(mg/mL)	% (w/v)
Acetylcysteine	200	20%	200	20%
Disodium Edetate	0.025	0.25%	0.05	0.5%
Sodium Hydroxide	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment
Hydrochloride Acid	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment

Review Comments:

1. The test product is solution intended for inhalation (mucolytic agent) or oral administration (acetaminophen antidote). It is **not** intended for injection.
2. The pH range of the test product is 6.0 to 7.5. The pH range of the RLD is also 6.0 to 7.5¹.
3. All inactive ingredients in the test product (b) (4) and the amount of Disodium Edetate is within IIG limits.
4. The amount of Disodium Edetate in the test product (b) (4) amount of Disodium Edetate used in the original RLD, Mucomyst® (NDA 013601).



5. According to the Division of Pulmonary and Allergy Drug Products Medical Officer Consultation³, the original RLD, Bristol Myers Squibb's Mucomyst® (NDA 013601), was not withdrawn due safety or efficacy concerns.
6. The formulation of the test product, InnoPharma, Inc.'s Acetylcysteine Solution, USP 20%, is adequate.

3.5 Waiver Request

Strengths for which waivers are requested	20%
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	WAIVER GRANTED
If not then why?	

3.6 Deficiency Comments

None.

3.7 Recommendations

1. The Division of Bioequivalence II (DB II) agrees that the information submitted by InnoPharma, Inc. demonstrates that Acetylcysteine Solution, USP, 20%, meets the requirements of Section 21 CFR § 320.22 (b) (3). The DB II recommends the waiver of bioequivalence testing be granted. Accordingly bioequivalence testing should not be undertaken.
2. The DB II deems the test product Acetylcysteine Solution, USP, 20%, manufactured by InnoPharma, Inc., to be bioequivalent to the reference product, Acetylcysteine Solution, 20%, manufactured by Luitpold.

3.8 Comments for Other OGD Disciplines

Discipline	Comment
N/A	

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 203853
APPLICANT: InnoPharma, Inc.
DRUG PRODUCT: Acetylcysteine Solution, USP, 20%

The Division of Bioequivalence II (DB II) has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

Appendix 5

Biopharmaceutics Inspection Request

OSI Consult Request for Biopharmaceutical Inspections	
Date	05/19/2015
Subject	Request for Biopharmaceutical Inspections (BE)
Addressed to	Sharon Turner-Rinehardt, RAC Team Lead (Acting), Project Management Team Office of Study Integrity and Surveillance sharon.turner-rinehardt@fda.hhs.gov
Consulting Office/Division	Office of New Drug Quality Assessment
Project Manager	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
Application Type	PEPFAR? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input checked="" type="checkbox"/> NDA <input type="checkbox"/> BLA <input type="checkbox"/> ANDA
Application Number	NDA 207916
Drug Product	AR10 (Acetylcysteine Effervescent Tablets for Oral Solution [0.5 g and 2.5 g])
Sponsor Name	Arbor Pharmaceuticals, LLC
Sponsor Address	Arbor Pharmaceuticals, LLC Attention: Allison Lowry Director, Regulatory Affairs 6 Concourse Parkway Suite 1800 Atlanta, GA 30328 Telephone: (404) 496-5903 Fax: (888) 777-1397
US Agent (if applicable)	n/a
US Agent Address	n/a
Electronic Submission	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
PDUFA Due Date	January 30, 2016
Action Goal Date	September 1, 2015
OSI Review Requested By	Mei Ou, Ph.D.

Inspection Request Detail (All fields should be fill out completely)	
Study #1	
Study Number	AR10.001
Study Title	An Open Label, Randomized, Two-Arm, Single-Dose, Two-Period, Crossover Study to Determine the Relative Bioavailability of AR10 (Acetylcysteine Effervescent Tablets for Oral Solution [0.5 g and 2.5 g]) as Compared to Reference Product (Acetylcysteine solution; Oral 20% [200mg/ml]) in Healthy Adult, Human Subjects, Under Fasting Conditions
Study Type	<input checked="" type="checkbox"/> In vivo BE <input type="checkbox"/> In vitro BE <input type="checkbox"/> Permeability <input type="checkbox"/> Others (specify)

<input type="checkbox"/> Inspection Request - Clinical Site	<input type="checkbox"/> Inspection Request - Analytical Site
Facility #1: Spaulding Clinical 525 S. Silverbrook Drive West Bend, Wisconsin 53095	Facility #1: (b) (4)
Clinical Investigator: Carlos Sanabria, MD (email) carlos.sanabria@spauldingclinical.com Tel: (262) 306-3085	Principal Analytical Investigator: (b) (4)
Facility #2 Name: (if applicable) Address: (Tel) (Fax)	Facility #2 Name: (if applicable) Address: (Tel) (Fax)
Clinical Investigator: (email)	Principal Analytical Investigator: (email)
Check one: <input checked="" type="checkbox"/> Routine inspection <input type="checkbox"/> For cause	Check one: <input checked="" type="checkbox"/> Routine inspection <input type="checkbox"/> For cause
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>	
<input checked="" type="checkbox"/> Study Report: (location: M5.3.1.2)	<input checked="" type="checkbox"/> Validation Report: (M5.3.1.2) <input checked="" type="checkbox"/> Bioanalytical Report: (M5.3.1.2)

Study #2				
Study Number				
Study Title				
Study Type	<input type="checkbox"/> In vivo BE	<input type="checkbox"/> In vitro BE	<input type="checkbox"/> Permeability	<input type="checkbox"/> Others (specify)
<input type="checkbox"/> Inspection Request - Clinical Site	<input type="checkbox"/> Inspection Request - Analytical Site			
Facility Name: (or indicate if same as above) Address: (Tel) (Fax)	Facility Name: (or indicate if same as above) Address: (Tel) (Fax)			
Clinical Investigator: (email)	Principal Analytical Investigator: (email)			
Check one: <input type="checkbox"/> Routine inspection <input type="checkbox"/> For cause	Check one: <input type="checkbox"/> Routine inspection <input type="checkbox"/> For cause			
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>				
<input type="checkbox"/> Study Report: (location, eg., 5.3.1.2)	<input type="checkbox"/> Validation Report: (eg., 5.3.1.2) <input type="checkbox"/> Bioanalytical Report: (eg., 5.3.1.4)			

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, OSI.

I. Appendix

Specific Items To be Addressed During the Inspection

1. Evaluate whether the study was conducted as per approved protocol (*i.e., the study subject recruitment followed the specified inclusion/exclusion criteria and dropouts followed the protocol's criteria and were properly documented*).
2. Evaluate whether protocol deviations were properly documented and justified.
3. Evaluate whether the blood/plasma samples were taken, stored, transported, and analyzed as per approved SOPs and the analytical and PK data analysis results were properly documented.
4. Evaluate whether the data excluded from the bioequivalence data analysis is justified.

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/s/

MEI OU
05/19/2015

Appendix 6

The OSIS recommendation letter of acceptance data without an on-site inspection for the Clinical Site (Spaulding Clinical, 525 S. Silverbrook Drive, West Bend, WI 53095)

MEMORANDUM

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

DATE: July 1, 2015

TO: Division of Gastroenterology Products (DGIEP)

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Recommendation to accept data without an on-site inspection

RE: NDA 207916

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as Voluntary Action Indicated (VAI). Although, the last inspection was classified as a VAI, the observations identified during the previous inspection had no impact on data reliability. Therefore based on the previous recommendation to the review division to accept the data for review, an inspection of the site will not be needed at this time.

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Clinical	Spaulding Clinical	525 S. Silverbrook Drive, West Bend, WI 53095

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/s/

SHILA S NKAH
07/01/2015

Appendix 7

The OSIS recommendation letter of acceptance the analytical data from study AR10.001 to be further reviewing by the Agency, after inspecting the Bioanalytical Site ([REDACTED] (b)(4))

MEMORANDUM

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

DATE: August 28, 2015

TO: Sarah Miksinski, Ph.D.
Director (Acting)
Office of New Drug Products
Office of Pharmaceutical Quality

FROM: Gajendiran Mahadevan, Ph.D.
Staff Fellow
Division of New Drug Bioequivalence (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

Xiaohan Cai, Ph.D.
Visiting Associate
Division of Generic Drug Bioequivalence (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Lead Pharmacologist
Division of New Drugs Bioequivalence Evaluation
Office of Study Integrity and Surveillance

and

Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence
Office of Study Integrity and Surveillance

SUBJECT: Surveillance inspection of [REDACTED] (b)(4)
[REDACTED] (b)(4) Covering NDA 207916, Acetylcysteine
Effervescent Tablets for Oral Solution (0.5g and 2.5
g), Arbor Pharmaceuticals, LLC., USA

At the request of the Office of New Drug Products (ONDP), the Office of Study Integrity and Surveillance (OSIS) inspected the analytical portion of the following bioavailability study:

Page 2 -Surveillance Inspection of [REDACTED]

(b) (4)

(b) (4)

Study Number: AR10.001

Study Title: "An open label, randomized, two-arm, single-dose, two-period crossover study to determine the relative bioavailability of AR10 (Acetylcysteine Effervescent Tablets for Oral Solution (0.5g and 2.5g) as compared to reference product (Acetylcysteine solution; oral 20% (200 mg/mL) in healthy adult, human subjects, under fasting conditions"

The analytical inspection was conducted during [REDACTED] at [REDACTED] by OSIS scientists Gajendiran Mahadevan, Ph.D. and Xiaohan Cai, Ph.D. The inspection included a thorough examination of study records, facilities and equipment, and interviews and discussions with the firm's staff and management.

(b) (4)

(b) (4)

At the conclusion of the inspection, Form FDA 483 was issued to the firm (**Attachment-1**). The firm responded to Form FDA 483 on August 21, 2015 (**Attachment-2**). The Form FDA 483, the firm's response to Form FDA 483, and our evaluation follow.

- 1) Study samples were not stored in a secure and controlled environment. Specifically, subject plasma samples were stored in an unlocked -80°C freezer located in an unsecured common area in the analytical facility.

Firm's Response: In their response to the Form FDA 483, [REDACTED] (b) (4) acknowledged the observation and promised to implement the following corrective actions by August 31, 2015.

(b) (4)

(b) (4)

1. Individual freezers holding study samples for FDA regulated studies will be locked.
2. Up to three employees will be assigned as freezer custodians and would control access to the samples in the locked freezers. Samples would also be tracked in Watson LIMS.
3. Key-card access will be implemented in the processing areas providing access to freezers by end of year 2015.
4. Standard Operating Procedures and policies of [REDACTED] will be updated to reflect the above changes.

(b) (4)

(b) (4)

OSIS Assessment: [REDACTED] (b) (4), s response is acceptable.

Following implementation, the corrective actions would provide physical security for study samples stored in freezers. During the inspection, we reviewed source documents for sample arrival and subject sample analysis and did not find any discrepancies. Thus, the above finding is unlikely to impact the integrity of the study data.

- 2) Computer system access was not limited to authorized individuals. Specifically, electronic source records were accessible to individuals from another establishment.

Firm's Response: [REDACTED] (b) (4) acknowledged the observation that the data servers were housed in an area accessible with their sister establishment, [REDACTED] (b) (4). However, they claimed that although some contractors had physical access to the room and data servers, logical access to the data servers and data was limited. As a corrective action, [REDACTED] (b) (4) stated that they are immediately limiting access to the server room to nine personnel: three representing the property management, two representing [REDACTED] (b) (4), and four representing [REDACTED] (b) (4). As a long-term fix for the physical security concerns of the data servers and data, the data servers will be physically relocated to a secured room in [REDACTED] (b) (4) facility by end of year 2015. Physical and logical access to the data and data servers would be limited. Standard Operating Procedures and policies of [REDACTED] (b) (4) will be updated to reflect the above changes.

OSIS Evaluation: Although access to the data generated from the above study had logical access controls, physical access to the data servers was not limited to authorized personnel of [REDACTED] (b) (4) and was also accessible to contractors and employees of [REDACTED] (b) (4). [REDACTED] (b) (4) did not have procedures in place to prevent accidental or intentional destruction/corruption of stored data. However, during the inspection, we did not note any discrepancies or missing data. Thus, the above finding is unlikely to impact the integrity of the study data.

Page 4 -Surveillance Inspection of [REDACTED]

(b) (4)

(b) (4)

Recommendations:

Following the evaluation of the inspectional findings and the firm's response, the analytical data from the audited study were found to be reliable. Therefore, we recommend that the analytical data from study AR10.001 be accepted for further Agency review.

Gajendiran Mahadevan, Ph.D.
OSIS, DNDBE

Xiaohan Cai, Ph.D.
OSIS, DGDBE

Final Classification:**VAI:**

(b) (4)

FEI#**E-mail CC:**

OSIS/Taylor/Dejernett/Fenty-Stewart/Nkha/Johnson

OSIS/DGDBE/Haidar/Skelly/Choi/Cai

OSIS/DNDBE/Bonapace/Dasgupta/Cho/Mahadevan

CDER/OPQ/ONDP/Miksinski/Ou

Draft: GM 08/18/2015; XC 08/24/2015;

Edit: AD 08/28/2015; CB 08/28/2015

OSI File: BE6906; O:\BE\EIRCOVER\207916. [REDACTED] (b) (4)

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical
Sites/[REDACTED] (b) (4) NDA 207916_Acetylcysteine

FACTS:

(b) (4)

Appendix 8

The revised labeling section 12.3 (pharmacokinetics) that was submitted by the Applicant on 10/06/2015:

12.3 Pharmacokinetics

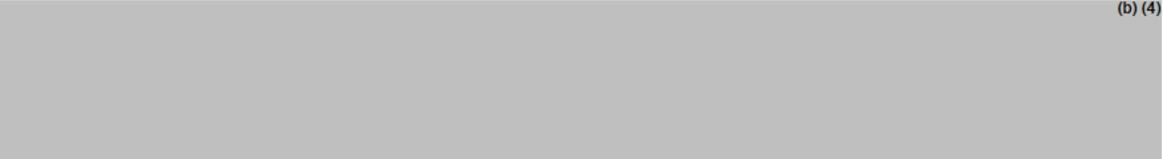
(b) (4)



Absorption

After administration of a single dose of CETYLEV (b) (4) (11 grams) dissolved in 300 mLs of water to healthy adult (b) (4) (n=29), mean (CV%) C_{max} was 26.5 (b) (4) mcg/mL and mean (CV%) AUC_{inf} was 186 (b) (4) hr•mcg/mL. Median (range) time to reach C_{max} was 2 (1.0 to 3.5) hours.

(b) (4)



Distribution

The volume of distribution (V (b) (4)
[redacted]

Elimination

Metabolism

Acetylcysteine (i.e., *N*-acetylcysteine) undergoes extensive first pass metabolism and is postulated to form (b) (4) *N,N*-diacetylcystine and *N*-acetylcysteine (b) (4) cysteine (b) (4) glutathione (b) (4) other metabolites.

Excretion

After a single oral dose of [³⁵S]-acetylcysteine 100 mg, between 13-38% of the total radioactivity administered was recovered in urine within 24 hours. (b) (4)
(b) (4) renal clearance was approximately 30% of total body clearance.

In healthy volunteers given a single oral CETYLEV dose of 11 grams the mean (CV%) terminal plasma half-life was 18.1 (21.9) hours.

Specific Populations

Hepatic Impairment

A (b) (4) intravenous 600 mg dose of acetylcysteine (b) (4) with (b) (4) hepatic impairment (b) (4) and 6 healthy matched controls. Systemic (b) (4) acetylcysteine exposure (mean AUC) increased 1.6-fold in (b) (4) with hepatic impairment compared to subjects with normal hepatic function.

Renal Impairment

Hemodialysis (b) (4) of total acetylcysteine. (b) (4)
[redacted]

[redacted] (b) (4)

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Overall Comments and Signature:

From Biopharmaceutics Perspectives:

- 1) No biowaiver issue is considered for the proposed two strengths;
- 2) The disintegration time of proposed effervescence tablets met the accepted specification for NMT ^(b)₍₄₎ minutes;
- 3) ANDA 203853 (20% acetylcysteine solution) is acceptable as reference drug in the submitted BE study for this NDA 207916 (acetylcysteine effervescence tablets);
- 4) The proposed BE study design is acceptable;
- 5) The background concentration of total acetylcysteine is considered to have minimally significant impact on the study results;
- 6) The proposed drug and the reference drug are shown to be "bioequivalent" after reassessment of the PK calculation by this reviewer; and
- 7) The Biopharmaceutics Inspections on both the Clinical Site (Spaulding Clinical) and the Bioanalytical Site (^(b)₍₄₎) are found acceptable.
- 8) In the Applicant's revised labeling section 12.3 (pharmacokinetics), the stated mean pharmacokinetic parameters, C_{max} , AUC_s , and plasma half-life ($T_{1/2}$) obtained from the BE study AR10.001 are reviewed and found acceptable. The rest of the labeling section 12.3 is currently under review by other disciplines.

This NDA 207916 for drug product, Acetylcysteine Effervescent Tablets, 500 mg and 2.5 g, is reviewed and found acceptable; therefore, this NDA 207916 is recommended for approval.

11/04/2015
Mei Ou, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Products

Mei Ou -S

Digitally signed by Mei Ou -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Mei Ou -S,
0.9.2342.19200300.100.1.1=2001622313
Date: 2015.11.10 08:57:24 -05'00'

Secondary Review Comments and Concurrence:

Concur

11/04/2015

Tien-Mien Chen, Ph.D.
Acting Biopharmaceutics Lead
Office of New Drug Products

Tienmien
Chen -S

Digitally signed by Tienmien Chen
-S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Tienmien Chen -S,
0.9.2342.19200300.100.1.1=13000
73135
Date: 2015.11.10 09:04:55 -05'00'

ASSESSMENT OF MICROBIOLOGY

17. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

The following microbial contamination tests and acceptance criteria, according to Table 13, are to be performed on each of the batches manufactured. Testing is performed on stability annually and at time of release per USP<61> and USP <62>.

Table 13 Microbiological Testing to be Performed

Microbial contamination	TAMC TYMC E. coli	≤ (b) ≤ (4)CFU/g CFU/g absent/g
--------------------------------	-------------------------	--

All registration batches demonstrated compliance with the limits and will continue to be tested per the acceptance criteria in Table 13. In addition, registration batches are tested for P. aeruginosa (absent/g), S. aureus (absent/g), and Salmonella (absent/10 g). In accordance with USP <1111> and stability data to date, required testing for solid oral dosage forms are total aerobic microbial count, total yeast and mold, and Escherichia coli. **Therefore, these tests and specifications are proposed for commercial batches.**

Reviewer's Assessment: Adequate

Microbiology testing is performed per the current USP General Chapter <61> and USP General Chapter <62>. In accordance with USP <1111> for Microbial Examination of Nonsterile Products, and based on stability data to date, the required testing for solid oral dosage forms are Total Aerobic Microbial Count, Total Yeast and Mold, and Escherichia Coli. Firm has included these tests and associated specifications are proposed for the commercial batches. *All registration batches (Sublots A & B for Batch # 028L13, 029L13 and 030L13 for 500 mg strength and Sublots A & B for Batch # 031L13, 031L13 and 033L13 for 2.5 g strength) demonstrate compliance with the limits.*

As an example, Batch Analysis Sub Lot A for Acetylcysteine Effervescent Tablets, 500 mg is provided below:

Batch Number		028L13-A	029L13-A	030L13-A
Test	Proposed Specification	Result	Result	Result

Microbial contamination	TAMC	≤ (b)(4)CFU/g	< (b)(4)CFU/g	< (b)(4)CFU/g	< (b)(4)CFU/g
	TYMC	≤ (b)(4)CFU/g	< (b)(4)CFU/g	< (b)(4)CFU/g	< (b)(4)CFU/g
	E. coli	Absent/g	Absent/g	Absent/g	Absent/g
	P. aeruginosa*	Absent/g	Absent/g	Absent/g	Absent/g
	S. aureus*	Absent/g	Absent/g	Absent/g	Absent/g
	Salmonella*	Absent/10 g	Absent/10 g	Absent/10 g	Absent/10 g

Firm states that compendial excipients (sodium bicarbonate USP, maltodextrin NF, sucralose NF, edetate disodium USP, and (b)(4)) used in the manufacture of Acetylcysteine Effervescent Tablets are tested by the analytical procedures of the respective USP/NF monographs. All compendial materials used in the manufacture of the proposed drug product will comply with the appropriate monographs and general USP/National Formulary (NF) requirements. Full testing in accordance with respective compendia will be performed or reduced testing may be implemented in accordance with the contract manufacturer's internal SOPs and GMPs.

Microbial contamination tests (Total Aerobic Microbial Count(≤ (b)(4) CFU/g), Total Yeast & Mold Count (≤ (b)(4) CFU/g), Escherichia coli(Absent/g) and Salmonella (Absent/g) are included for the Lemon Flavor and Peppermint flavor excipients.

It is noted that stability protocol includes microbial testing at T₀ Please see below.

1.2 Stability Protocol in Support of Acetylcysteine Effervescent Tablets

Table 3: Stability Protocol for Acetylcysteine Effervescent Tablets in 2-Count Blister Packs (500 mg and 2.5 g) – NDA Registration Batches

Time point (months)		0	1 ^a	2 ^a	3	6	9	12	18	24	36	
Strengths	500 mg	028L13	T,M	T	T	T	T	T	T,M	T	T,M	T,M
		029L13	T,M	T	T	T	T	T	T,M	T	T,M	T,M
		030L13	T,M	T	T	T	T	T	T,M	T	T,M	T,M
	2.5 g	031L13	T,M	T	T	T	T	T	T,M	T	T,M	T,M
		032L13	T,M	T	T	T	T	T	T,M	T	T,M	T,M
		033L13	T,M	T	T	T	T	T	T,M	T	T,M	T,M

Key:
 T= Unless noted otherwise, tested for Blisters appearance, Tablets appearance, Average weight, Uniformity of dosage units, Disintegration time, (b)(4) pH, Hardness, Identification by HPLC, Identification by IR, Assay, Related substances, Seal test
 Identification will only be performed at T=0
 M = Microbial testing
^a 40°C/75%RH testing only

Firm has provided bulk holding time studies for Batch # 030L13 (500 mg strength) and Batch # 033L13 (2.5 g strength) for (b)(4) months at long term stability conditions which also contains microbial contamination data at initial and (b)(4) month period and data provided meet the proposed criteria.

Information provided is adequate.

2.3.P.7 Container/Closure System

18. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:

Not applicable as drug product is in solid oral dosage form and non-sterile in nature.

Reviewer's Assessment: Adequate

(b) (4)

(b) (4)

This section may have been reviewed by drug product reviewer in 2.3.P.7.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

19. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: N/A

Reviewer's Assessment: N/A

20. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: N/A

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

Microbiology testing is performed per the current USP General Chapter <61> and USP General Chapter <62>. In accordance with USP <1111> for Microbial Examination of Nonsterile Products, and based on stability data to date, the required testing for solid oral dosage forms are Total Aerobic Microbial Count, Total Yeast and Mold, and Escherichia Coli. Firm has included these tests and associated specifications are proposed for all commercial batches at release. All registration batches (Sublots A & B for Batch # 028L13, 029L13 and 030L13 for 500 mg strength and Sublots A & B for Batch # 031L13, 031L13 and 033L13 for 2.5 g strength) demonstrate compliance with the limits.

Information provided in microbiology section is adequate.

Vaikunth S. Prabhu (Primary reviewer) – August 23, 2015

Vaikunth S. Prabhu -S

Digitally signed by Vaikunth S Prabhu S
DN: c US o U.S. Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 1300395643 cn Vaikunth S Prabhu S
Date: 2015.11.09 13:51:16 -0500

Secondary Review Comments and Concurrence:

I concur, the overall assessment for microbiology is adequate.

Celia N. Cruz, Ph.D. , August 26, 2015
Acting Branch Chief, OPF/DPAII/BV

Celia Cruz -S

Digitally signed by Celia Cruz S
DN: c US o U.S. Government ou HHS ou FDA ou People
cn Celia Cruz S 0 9 2342 19200300 100 1 1 2000473041
Date: 2015.11.11 09:03:28 -0500

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

21. Is the applicant's claim for categorical exclusion acceptable? Yes

22. Is the applicant's Environmental Assessment adequate for approval of the application? NA

Applicant's Response:

Reviewer's Assessment: Acetylcysteine, an acetaminophen antidote, is the N-acetyl derivative of the naturally-occurring amino acid, cysteine and undergoes extensive first pass metabolism. Acetylcysteine does not appear to have estrogenic, androgenic, or thyroid hormone pathway activity. Non-clinical studies indicate low reproductive toxicity and no teratogenic effects. The reviewer found no information to indicate 'extraordinary circumstances'. The application meets criteria for minimal environmental risk.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: The cited categorical exclusion at 21 CFR 25.31(b) is appropriate for the anticipated amount of drug to be used, and a statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable.

Raanan A. Bloom, Ph.D./OPQ/ONDP/IO

Raanan A.
Bloom -S

Digitally signed by Raanan A. Bloom -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300062595,
cn=Raanan A. Bloom -S
Date: 2015.11.10 07:54:02 -05'00'

Secondary Review Comments and Concurrence:

I concur
Scott Furness, Ph.D., Deputy Director/ONDP

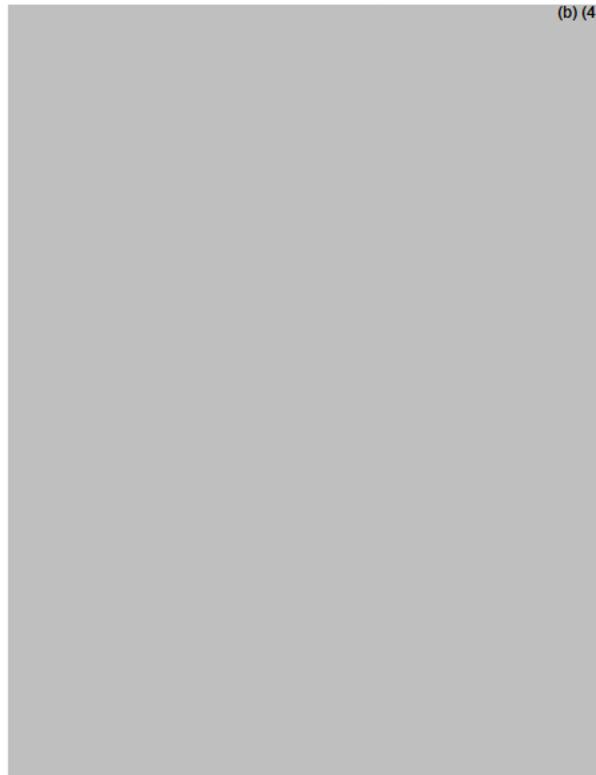
Michael S.
Furness -S

Digitally signed by Michael S. Furness -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People,
0.9.2342.19200300.100.1.1=1300153233,
cn=Michael S. Furness -S
Date: 2015.11.10 08:40:33 -05'00'

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1
A. Labeling & Package Insert

Carton and Container Labels

Immediate container labels – 2-count Blister



Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The drug name is not presented correctly. Not Satisfactory
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Displayed as 500 mg and 2.5 g. Satisfactory
Net contents (21 CFR 201.51(a))	Net content not displayed. Not Satisfactory
“Rx only” displayed prominently on the main panel	The statement is not displayed due to small size of the blister pack. Not Satisfactory
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC numbers are indicated properly. Satisfactory
Lot number and expiration date (21 CFR 201.17)	Displayed Satisfactory
Storage conditions	Storage condition is not displayed due to small

	size of the blister Satisfactory
Bar code (21CFR 201.25)	Barcode is not displayed due to small size of blister pack. Satisfactory
Name of manufacturer/distributor	The names of manufacturer and distributor are displayed correctly. Satisfactory
And others, if space is available	N/A

Evaluation: Not adequate. The 2-count blister pack labels should be revised as follows:

- 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”

Carton labels

500 mg 10-tablet carton

(b) (4)



2.5 g 10-tablet carton

(b) (4)



Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size, prominence) (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Proprietary name and established name are correctly described. Satisfactory
Dosage strength (21CFR 201.10(d)(1), 21CFR 201.100(b)(4))	Displayed as 500 mg or 2.5 g Satisfactory
Net quantity of dosage form (21 CFR 201.51(a))	Displayed on the carton. Satisfactory
“Rx only” displayed prominently on the main panel (21 CFR 201.100 (b)(1))	The statement is displayed on the carton. Satisfactory
Expiration date and lot number (21 CFR 201.17 and 21 CFR 201.18)	Lot and Exp are displayed. Satisfactory
Storage conditions	Storage condition is described on the carton. Satisfactory
Bar code (21CFR 201.25)	Bar code displayed correctly Satisfactory
NDC number (21 CFR 201.2, 21 CFR 207.35(b)(3)(i))	NDC number displayed correctly Satisfactory
Manufacturer/distributor's name (21CFR201.1(a))	The name of manufacturer is correctly described. Satisfactory
The list of inactive ingredients, 21CFR 201.10(a), if not oral dosage form; and quantitative ingredient information, if parenteral injection. 21CFR 201.100(b)(5)(iii)	The inactive ingredients are not displayed which is acceptable because this is an oral tablet. Satisfactory
Statement of being sterile (if applicable)	N/A
“See package insert for dosage information” (21 CFR 201.55)	This statement is correctly displayed as (b) (4) Satisfactory
“Keep out of reach of children” (Required for OTC but Optional for Rx drugs)	Displayed Satisfactory
Route of Administration (21 CFR 201.100(b))	N/A

Evaluation: Adequate. The container carton labels for 10-tablet and 20-tablet cartons for 500 mg and 2.5 g tablets are adequate.

Labeling Review

The following is a summary of the labeling review.

1. Package Insert

(a) “Highlights” Section (21CFR 201.57(a))

HIGHLIGHTS OF PRESCRIBING INFORMATION
 These highlights do not include all the information needed to use CETYLEV™ safely and effectively. See full prescribing information for CETYLEV.

CETYLEV (acetylcysteine) effervescent tablets for oral solution
 Initial U.S. Approval: 1963

DOSAGE FORMS AND STRENGTHS
 Effervescent tablets, 0.5 grams and 2.5 grams (3)

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	CETYLEV (acetylcysteine) effervescent tablets, for oral solution	The drug product title is described correctly. Satisfactory
Dosage form, route of administration	effervescent tablets, for oral solution	Satisfactory
Controlled drug substance symbol (if applicable)		Not applicable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Effervescent tablets, 0.5 grams and 2.5 grams	The dosage form is described as tablets is correct. The strength is not described correctly. Not Satisfactory
Whether the drug product is scored (If the product is not scored, do not say “not scored.”)		The product is not scored.

Evaluation: Not Adequate. The dosage strengths should be revised as follows:

- 0.5 g should be revised to 500 mg

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3 DOSAGE FORMS AND STRENGTHS

CETYLEV effervescent tablets are supplied as white, round, flat tablets with a lemon mint (b) (4) in the following dosage strengths:

- 0.5 gram tablets debossed "T" on one side.
- 2.5 gram tablets debossed "O" on one side.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Effervescent tablets	Dosage forms described correctly. Satisfactory
Strengths: in metric system	0.5 g and 2.5 g	The strengths are described correctly. Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	white, round, flat tablets with a lemon mint (b) (4) in the following dosage strengths: <ul style="list-style-type: none"> • 0.5 gram tablets debossed "T" on one side. • 2.5 gram tablets debossed "O" on one side. 	The tablets are described correctly. Tablet strength is not described correctly Not Satisfactory

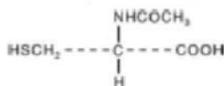
Evaluation: Not Adequate. The dosage strengths should be revised as follows:

- 0.5 g should be revised to 500 mg

#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION

Acetylcysteine, (b) (4) is the N-acetyl derivative of the naturally-occurring amino acid, cysteine. (b) (4) is a white crystalline powder with the molecular formula C₅H₉NO₃S, a molecular weight of 163.2, and chemical name of N-acetyl-L-cysteine. Acetylcysteine has the following structural formula:



CETYLEV effervescent tablets contain the following inactive ingredients: sodium bicarbonate, maltodextrin, lemon flavor, sucralose, peppermint flavor, and edetate disodium.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	CETYLEV and acetylcysteine	The proprietary name and established name are correct.
Dosage form and route of administration	Effervescent tablets	Satisfactory
Active moiety expression of strength with equivalence statement for salt (if applicable)	Not applicable	Not applicable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	sodium bicarbonate, maltodextrin, lemon flavor, sucralose, peppermint flavor, and edetate disodium	Information for inactive ingredients is provided correctly. Satisfactory
Statement of being sterile (if applicable)		Not applicable
Pharmacological/ therapeutic class		Will be determined in the labeling meeting. Satisfactory
Chemical name, structural formula, molecular weight	Chemical Name: N-acetyl-L-cysteine Molecular formula: C ₅ H ₉ NO ₃ S Molecular weight: 163.2 molecular structure is: $ \begin{array}{c} \text{NHCOCH}_3 \\ \\ \text{HSCH}_2 - \text{C} - \text{COOH} \\ \\ \text{H} \end{array} $	This information is correct. Satisfactory

If radioactive, statement of important nuclear characteristics.		Not applicable
Other important chemical or physical properties (such as pKa, solubility, or pH)	White powder	The solubility of the drug substance in various solvents is not described. Not Satisfactory

Evaluation: No adequate. Sec. 11. Description section should be revised to include chemical or physical properties such as solubility. The tablet strength 0.5 g should be revised to 500 mg

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 HOW SUPPLIED/STORAGE AND HANDLING

CETYLEV effervescent tablets are supplied as white, round, flat tablets with a lemon mint smell packaged in 2-count peelable foil blister packs in the following dosage strengths:

- 500 mg tablets debossed "T" on one side; Each carton containing 2-count blister packs (24338-700-02)
 - NDC 24338-700-05: 5 pack carton containing 10 tablets
 - NDC 24338-700-10: 10 pack carton containing 20 tablets
- 2.5 g tablets debossed "O" on one side; Each carton containing 2-count blister packs (24338-725-02)
 - NDC 24338-725-05: 5 pack carton containing 10 tablets
 - NDC 24338-725-10: 10 pack carton containing 20 tablets

(b) (4)

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature.] Protect from moisture. Store tablets in original blister package until use.

Dilutions of acetylcysteine should be used freshly prepared and utilized within two hours.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	500 mg and 2.5 g	The strengths should be consistent as 0.5 g and 2.5 g Not Satisfactory
Available units (e.g., bottles of 100 tablets)	10 tablets and 20 tablets	This information provided. Satisfactory

<p>Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number</p>	<p>CETYLEV effervescent tablets are supplied as white, round, flat tablets with a lemon mint smell packaged in 2-count peelable foil blister packs</p> <ul style="list-style-type: none"> • 500 mg tablets debossed “T” on one side; Each carton containing 2-count blister packs (24338-700-02) • NDC 24338-700-05: 5 pack carton containing 10 tablets • NDC 24338-700-10: 10 pack carton containing 20 tablets • 2.5 g tablets debossed “O” on one side; Each carton containing 2-count blister packs (24338-725-02) • NDC 24338-725-05: 5 pack carton containing 10 tablets • NDC 24338-725-10: 10 pack carton containing 20 tablets 	<p>The description of tablets and NDC numbers are provided. However, the strength was 0.5 g tablets was not correctly described.</p> <p>Not Satisfactory</p>
---	--	---

<p>Special handling (e.g., protect from light, do not freeze)</p>		<p>Not applicable</p>
<p>Storage conditions</p>	<p>Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature.] Protect from moisture. Store tablets in original blister package until use. Dilutions of acetylcysteine should be used freshly prepared and utilized within two hours.</p>	<p>Information not provided correctly.</p> <p>Not Satisfactory</p>

Evaluation: Not adequate. The 16. How supplied and Handling section should be revised as follows:

- To be consistent throughout the PI the strengths of the effervescent tablets should be 0.5 and 2.5 g

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured for: Atlanta, GA 30328	Information is correctly provided.
	Made in Switzerland	Satisfactory

II. List of Deficiencies To Be Communicated

A. Regarding Label/labeling

1. Immediate container labels:

- 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”

2. PI

Highlights of Prescribing Information

The dosage strength should be revised as follows:

- 0.5 g should be revised to 500 mg

3 Dosage Forms and Strengths

- The tablet strength 0.5 g should be revised to 500 mg

#11 Description

- Include chemical or physical properties including solubility of the drug substance in this section
- The tablet strength 0.5 g should be revised to 500 mg

#16 How supplied/storage and handling

- The tablet strength 0.5 g should be revised to 500 mg

III. Attachments

A. Facilities:

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
(b) (4)	(b) (4)	CSN: Manufacturing, Testing	No PAI recommended	Low	Acceptable based on inspectional history and experience
		CTL: Testing (micro)	No PAI recommended	Medium (previous OAI considered)	Acceptable based on inspectional history and experience
		CTL: Testing (release)	No PAI recommended	Low	Acceptable based on inspectional history and experience

Overall Recommendation: “Approve” recommendation was entered in Panorama on November 06, 2015.

Submission Facility Status View

Facility Alerts
 This report displays the Alerts associated with facilities on the selected applications

No active OAI / POAI Alerts are present against the facilities on selected Projects

[Refresh](#)

Facility Status View for NDA 207916 Original 1
 Displays information for the facilities that are associated to NDA 207916 Original 1. It also shows the Overall Manufacturing Inspection Recommendation for the application and the associated OPF Facility Recommendations.
 Time run: 11/8/2015 7:58:28 PM

Overall Manufacturing Inspection Recommendations for NDA 207916 Original 1

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Completion Date
NDA 207916-Orig1-New - Form 3674 - User Fee/NDA - Coversheet(2)	ARBOR PHARMACEUTICALS LLC	Approve	Complete	11/6/2015

OPF Facility Recommendations for Facilities on NDA 207916 Original 1

Project Name	FEI	DIINS	Facility Name	Profile	OPF Facility Recommendation	OPF Facility Recommendation Task Status	OPF Facility Recommendation Task Completion date
NDA 207916-Orig1-New - Form 3674 - User Fee/NDA - Coversheet(2)			(b) (4)	CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	(b) (4)
NDA 207916-Orig1-New - Form 3674 - User Fee/NDA - Coversheet(2)	3004311700	481608818	ALPEX PHARMA SA	TCM TABLETS, PROMPT RELEASE	Approve Facility	Complete	11/6/2015
NDA 207916-Orig1-New - Form 3674 - User Fee/NDA - Coversheet(2)			(b) (4)	CSN NON-STERILE API BY CHEMICAL SYNTHESIS	Approve Facility	Complete	(b) (4)
NDA 207916-Orig1-New - Form 3674 - User Fee/NDA - Coversheet(2)			(b) (4)	CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	(b) (4)

Data refreshed on: 11/07/15 12:15:30 AM

B. Lifecycle Knowledge Management

a) Drug Product

Product Attribute / CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	LifeCycle consideration/Comments
Blister and tablet Appearance	Blister sealing and moisture	M to L	<p>Blisters and tablets are visually inspected for swelling or deterioration.</p> <p>(b) (4)</p>	<p>During the stability testing no blister or DP deterioration was found.</p> <p>Low to None</p>	None
Assay	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L	<p>Assay is determined by a validated HPLC method.</p> <p>(b) (4)</p> <p>The long-term and accelerated stability studies of the registration batches demonstrated that there is no significant change in the quality of the DP during the time tested</p>	<p>The drug product is expected to be safe for oral administration during the entire shelf life from product quality perspective.</p> <p>Low to None</p>	None
Related Substances Impurities / Degradants	<ul style="list-style-type: none"> • Raw materials • Process parameters • Container/closure system 	L	<p>The related substances/ impurities are fully characterized and controlled by DS specification. The impurities are also controlled by DP specification at</p>	<p>(b) (4)</p>	None

			release and on stability. The impurities are assessed by validated HPLC methods.	The impurities were within the specification in the registration batches. Low to None	
(b) (4)					
Disintegration	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L	(b) (4) The disintegration of the of the DP is controlled by DP specification.	Low to None	None
Hardness	<ul style="list-style-type: none"> • Process parameters 	M to L	(b) (4) Hardness is also controlled in the DP specification.	All of the registration batches met DP hardness specification at release and stability. Low to None	None

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 207916

Submission Type: Standard

Established/Proper Name:
Acetylcysteine

Applicant: Arbor
Pharmaceuticals, LLC

Letter Date: March 30, 2015

Dosage Form: Effervescent tablets

Chemical Type: 3
(new dosage form)

Stamp Date: March 30, 2015

Strength: 0.5g and 2.5g

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.		X	There are no filing issues.
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?		X	There are no comments to convey to the applicant.

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.	Botanical ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.	Naturally-derived Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.	PET Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.	PEPFAR Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.	Sterile Drug Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
8.	Transdermal ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Pediatric form/dose ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Locally acting drug ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
11.	Lyophilized product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	First generic ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Solid dispersion product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
14.	Oral disintegrating tablet ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Modified release product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
16.	Liposome product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Biosimilar product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
18.	Combination Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
19.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment	
Regulatory Considerations					
20.	USAN Name Assigned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Acetylcysteine	
21.	End of Phase II/Pre-NDA Agreements	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
24.	Comparability Protocol(s) ²	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
25.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Quality Considerations					
26.	Drug Substance Overage	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
27.	Design Space	Formulation	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
28.		Process	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
29.		Analytical Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
30.		Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
31.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
32.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
33.	Alternative Microbiological Test Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
34.	Process Analytical Technology ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	<input type="checkbox"/>	<input type="checkbox"/>	
36.		Excipients	<input checked="" type="checkbox"/>	<input type="checkbox"/>	In-house methods are used for lemon and peppermint flavors.
37.		Microbial	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
38.	Unique analytical methodology ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
39.	Excipients of Human or Animal Origin	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
40.	Novel Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
41.	Nanomaterials ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
42.	Hold Times (b) (4)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Bulk tablets may be stored up to (b) (4) months	
43.	Genotoxic Impurities or Structural Alerts	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
44.	Continuous Manufacturing	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
45.	Other unique manufacturing process ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
47.	New delivery system or dosage form ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
48.	Novel BE study designs	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
49.	New product design ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
50.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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FILING REVIEW

C. FILING CONSIDERATIONS				
	review? <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <ul style="list-style-type: none"> <input type="checkbox"/> Facilities and Equipment <input type="checkbox"/> Adventitious Agents Safety Evaluation <input type="checkbox"/> Novel Excipients <input type="checkbox"/> Regional Information <ul style="list-style-type: none"> <input type="checkbox"/> Executed Batch Records <input type="checkbox"/> Method Validation Package <input type="checkbox"/> Comparability Protocols 			
FACILITY INFORMATION				
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: <ul style="list-style-type: none"> <input type="checkbox"/> Name of facility, <input type="checkbox"/> Full address of facility including street, city, state, country <input type="checkbox"/> FEI number for facility (if previously registered with FDA) <input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person. <input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and <input type="checkbox"/> DMF number (if applicable) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <ul style="list-style-type: none"> <input type="checkbox"/> Is a manufacturing schedule provided? <input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle? 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
DRUG SUBSTANCE INFORMATION				
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

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FILING REVIEW

C. FILING CONSIDERATIONS				
	<input type="checkbox"/> general information <input type="checkbox"/> manufacture <ul style="list-style-type: none"> ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment 			
DRUG PRODUCT INFORMATION				
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <ul style="list-style-type: none"> <input type="checkbox"/> Description and Composition of the Drug Product <input type="checkbox"/> Pharmaceutical Development <ul style="list-style-type: none"> ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development <input type="checkbox"/> Manufacture <ul style="list-style-type: none"> ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? <input type="checkbox"/> Control of Excipients 	☒	☐	☐

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C. FILING CONSIDERATIONS					
	<input type="checkbox"/> Control of Drug Product <ul style="list-style-type: none"> ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution <input type="checkbox"/> Reference Standards or Materials <input type="checkbox"/> Container Closure System <ul style="list-style-type: none"> ○ Include data outlined in container closure guidance document <input type="checkbox"/> Stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment <input type="checkbox"/> APPENDICES <input type="checkbox"/> REGIONAL INFORMATION				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: <ul style="list-style-type: none"> • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided? 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<ul style="list-style-type: none"> • YES: The comparative BA/BE study is entitled as AR10.001: An Open Label, Randomized, Two-Arm, Single-Dose, Two-Period, and Crossover Study in Healthy Adult, Human Subjects, under Fasting Condition. • YES • YES: OSI request for Biopharmaceutical Inspections is needed (or is going to be requested), for both clinical site and analytical site inspection.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The to-be-marketed formulation was employed in the above BE study No. AR10.001.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

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C. FILING CONSIDERATIONS					
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <ul style="list-style-type: none"> <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production <input type="checkbox"/> novel excipients 	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Are the following information available for Biotech Products: <ul style="list-style-type: none"> <input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: <ul style="list-style-type: none"> o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			<input checked="" type="checkbox"/>	

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Drug Substance and Drug Product Summary

Acetylcysteine, USP is manufactured by [REDACTED]^{(b) (4)}. The detailed CMC information is provided in DMF [REDACTED]^{(b) (4)}. The DMF was reviewed by Dr. Xavier J. Ysern on April 27, 2015 for this application and deemed adequate.

The drug product, acetylcysteine effervescent tablet, is indicated to prevent or lessen hepatic injury [REDACTED]^{(b) (4)} injection of potentially hepatotoxic quantity of acetaminophen. The drug product is supplied as 0.5 g and 2.5 g effervescent tablets. Each effervescent tablet contains 0.5 g or 2.5 g of active ingredient, acetylcysteine, USP. The other inactive ingredients are sodium bicarbonate, maltodextrin, sucralose, edetate disodium, lemon and peppermint flavors. The 0.5g effervescent tablets are debossed with “I” on one side and the 2.5 g effervescent tablets are debossed with “O” on one side. The white, round, flat effervescent tablets are packaged in blister packs. Each blister contains 2 effervescent tablets in separate cavities. The applicant has provided stability data for three registration batches of both strength tablets. Based on the stability results the applicant has proposed 24-month expiration dating period.

Acetylcysteine, USP is manufactured by [REDACTED]^{(b) (4)}. The detailed CMC information is provided in DMF [REDACTED]^{(b) (4)}. The DMF was reviewed by Dr. Xavier J. Ysern on April 27, 2015 for this application and deemed adequate.

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FILING REVIEW

Biopharmaceutics Section Brief Summary (No filing Issues to be included in the 74-Day letter)

1. Submission summary

The Applicant, Arbor Pharmaceuticals, LLC, submitted this original NDA-207916 on 03/30/2015 for Acetylcystein Effervescent Tablets (CETYLEV), 500mg and 2.5g, for the indication as an antidote to prevent or lessen hepatic injury (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen.

This is a 505(b)(2) application. A comparative bioavailability/bioequivalence (BA/BE) study AR10.001 was submitted. The purpose of AR10.001 was to bridge proposed acetylcystein effervescent tablets (CETYLEV) for oral solution to the reference listed drug (RLD) Mucomyst solution (NDA 13601).

2. A brief description of submitted BA/BE study

The submitted BA/BE study AR10.001 is entitled “An Open Label, Randomized, Two-Arm, Single-Dose, Two-Period, Crossover Study to Determine the Relative Bioavailability of AR10 (Acetylcysteine Effervescent Tablets for Oral Solution [0.5 and 2.5 g]) as Compared to Reference Product (Acetylcysteine solution; Oral 20% [200mg/ml]) in Healthy Adult, Human Subjects, Under Fasting Conditions”. It is a standard single-center, open-label, randomized, two-arm, single-dose, two-period, crossover relative bioavailability study involving healthy fasting subjects to compare the relative bioavailability of a single dose of CETYLEV acetylcysteine effervescent tablets (code named AR10) in oral solution versus the RLD acetylcysteine oral 20% solution diluted per labeling.

The reference product used in AR10.001 was Acetylcysteine 20% (200 mg/mL) (Innopharma ANDA 203853). Since Mucomyst solution was discontinued in 2009 and was unavailable, (b) (4)

(b) (4) the Agency agreed (FDA minutes dated 27Feb2013, page 4, PIND 116902) that an AN rated acetylcysteine solution product (therapeutic equivalent code for solutions and powders for aerosolization) could be used as the marketed equivalent of the RLD in AR10.001. Therefore, the reference product (FDA-approved under Innopharma ANDA 203853) used in AR10.001 BE study was a marketed acetylcysteine solution product rated AN in compliance with this FDA feedback.

3. Disintegration method description and brief summary

The Applicant introduced the Disintegration study for proposed drug product. The product is designed to dissolve in water and the relevant physical property and specification that impacts and controls product performance is set as Disintegration (effervescence) time (NMT^{(b) (4)} minutes).

Disintegration (effervescence) time testing is performed according to (b) (4) method 12101115. According to USP <701>, Disintegration, does not contain criteria for effervescent tablets; therefore, the proposed acceptance limit of NMT^{(b) (4)} minutes is based on (b) (4)

(b) (4) Current release and stability testing results are within the acceptance limit and range from (b) (4) for 2.5 g.

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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=20003
48333, cn=Hitesh N. Shroff -S
Date: 2015.05.29 14:05:20 -04'00'

Hitesh Shroff, Ph. D.
Reviewer, Branch V/DNDP II
ONDP