CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215040Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: **January 29, 2024**
From: **Hamid Shafiei, Ph.D.**
Application Technical Lead, Branch IV
Division of New Drug Products II
Office of New Drug Products

To: **To Executive Summary, IQA for Assessment # 1 of NDA 215040**

Subject: **ONDP Recommendation - Approval**

During the first cycle review of this application, labeling negotiation with the application was not pursued due to the intended complete response for this application from the clinical perspective. Therefore, in IQA dated April 3, 2024, this application was not recommended for approval from the OPQ perspective until successful labeling negotiation is conducted and labeling issues are adequately addressed. The applicant resubmitted this applicant on August 14, 2023 and responded to the complete response.

This resubmission did not include any CMC update and no additional OPQ review for this application except the labeling was needed. During the second cycle review of this application, the labeling negotiation was pursed. The CMC labeling deficiencies that were delineated in the labeling review by the Dr. Caroline Strasinger were communicated to applicant. The applicant has submitted the PI labeling on January 24, 2024 and container closure and carton labels on January 25, 2024 that has adequately addressed all CMC labeling/labels deficiencies. Dr. Strasinger's labeling review is attached to this memorandum. However, for brevity the PI labeling and container closure and carton labels are not attached to this document and is referred to the applicant submissions (SDN 19 and SDN 20) in DocuBridge dated January 24 and January 25, 2024.

Therefore, this application is now recommended for **approval** with an expiration dating period of **24 months**.

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 1/29/2024 01:19:46PM
GUID: 507d824300005f344cf8b5e5989f0057

Title:	NDA IQA Template CHAPTER IV-LABELING
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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	215040
Assessment Cycle Number	2
Drug Product Name	LEGUBETI (acetylcysteine) for oral solution

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	Pending concurrence from Applicant (comments to be conveyed 19-JAN-2024)
Patient Information	Adequate	Pending concurrence from Applicant (comments to be conveyed 19-JAN-2024)
Instruction for Use (IFU)	Choose an item.	N/A
Container Labels	Adequate	Pending concurrence from Applicant (comments to be conveyed 19-JAN-2024)
Carton Labeling	Adequate	Pending concurrence from Applicant (comments to be conveyed 19-JAN-2024)

Brief Description of Outstanding Issues:

The Labeling and Label of NDA 215040 **is ADEQUATE from the OPQ perspective, pending the Applicant's concurrence** with the Labeling and Label comments to be conveyed on 19-JAN-2024. (The OPQ recommendations were provided to OND on 4-DEC-2023).

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
eCTD 16, SDN 0017	14-AUG-2023	PI, Carton/Container

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	LEGUBETI (acetylcysteine) for oral solution
Route(s) of administration	Adequate	oral
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Inadequate	Per USP, (b) (4) should be removed and just "For oral solution: 500 mg and 2.5 grams of acetylcysteine Communicated to OND 4-DEC-23

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline

[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	Inadequate	Add of acetylcysteine Communicated to OND 4-DEC-23
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8]	N/A	

Assessment: *Inadequate*

All deficiencies were communicated to OND on 04-DEC-2023. Once agreed to by the applicant, the labeling for Highlights is adequate.

[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

(b) (4)

	(choose “Adequate”, “Inadequate”, or “N/A”)	**mments** rovide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	Adequate	Instructions included for dissolving with water and diet cola (both vehicles supported by CMC information).
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	Instructions to consume immediately, in its entirety within one hour.
For parenteral products: include statement: *“Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.”*[11]	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may	N/A	

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)
[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments
[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
be applicable to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: *Inadequate*

Applicant was requested to replace the term (b) (4) with "packet" throughout the label and labeling. OPPQ confirmed (b) (4) was an outdated term, and that packet is the proper container closure description on November 28, 2023 via email.

The request to use the term packet instead of (b) (4) throughout label and labeling was communicated to OND on 04-DEC-2023. Once agreed to by the applicant, the labeling for Dosage and Administration is adequate.

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3 DOSAGE FORMS AND STRENGTHS

(b) (4)

	(choose "Adequate", "Inadequate", or "N/A")	(If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Inadequate	Formatting changes requested

[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
		Communicated to OND 4-DEC-23
Strength(s) in metric system	Inadequate	Formatting changes requested Communicated to OND 4-DEC-23
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	Inadequate	Add "of acetylcysteine" Communicated to OND 4-DEC-23
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Inadequate	Formatting changes requested Communicated to OND 4-DEC-23
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Assessment: *Inadequate*

All deficiencies were communicated to OND on 04-DEC-2023. Once agreed to by the applicant, the labeling for Dosage Forms and Strengths is adequate.

1.2.3 Section 11 (DESCRIPTION)[14]

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

(b) (4)

Item	Labeling (choose "Adequate", "Inadequate", or "N/A")	(If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	LEGUBETI (acetylcysteine) for oral solution
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	For oral solution
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	Adequate	For clarity OND/DMEPA requested units to match per each strength (2.5 grams acetylcysteine equivalent to 4.74 grams of acetylcysteine lysine) throughout labeling. This requested change is acceptable from the OPQ perspective.
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	povidone

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	Antidote for acetaminophen overdose
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	Add freely soluble in water
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

Assessment: *Adequate*

The Description section of labeling is adequate. The requested change from OND/DEMPA to use grams is acceptable from the OPQ perspective.

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(b) (4)

	(choose "Adequate", "Inadequate", or "N/A")	**sor's Comments** dequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Inadequate	Remove (b) (4) Communicated to OND 4-DEC-23
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is	Inadequate	Edited for clarity; add acetylcysteine Communicated to OND 4-DEC-23

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
based on the active moiety. No equivalency statement.		
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Inadequate	Edited for clarity; correct to packets Communicated to OND 4-DEC-23
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	Inadequate	Edited for clarity Communicated to OND 4-DEC-23
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Inadequate	Edited for clarity Communicated to OND 4-DEC-23
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber*	N/A	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
latex. Avoid statements such as "latex-free."[21]		
Include information about child-resistant packaging[22] (if chosen by manufacturer).	N/A	

Assessment: *Inadequate*

All deficiencies were communicated to OND on 04-DEC-2023. Once agreed to by the applicant, the labeling for How Supplied/Storage is adequate.

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	Galephar Pharmaceutical Research Inc. Humacao, 00791, Puerto Rico, USA

Assessment: *Adequate*

2.0 PATIENT LABELING

atient Labeling (e.g., Medication

(b) (4)

orm Users that the Product or Product
)

[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)
[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues. as appropriate)
Established name[24]	Inadequate	Remove (b) (4)
Special preparation instructions (if applicable).	Adequate	
Storage and handling information (if applicable).	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	N/A	
Active ingredient(s) (if applicable).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Inadequate*

The deficiency to correct the established name was communicated to OND on 4-DEC-2023. Once agreed to by the applicant, the patient information is adequate.

3.0 CONTAINER AND CARTON LABELING[25]

[24] Established name = [Drug] [Route of Administration] [Dosage Form]
[25] Carton and Container Labeling Resources

3.

[26] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

	(choose “Adequate”, “Inadequate”, or “N/A”)	**as that of Carton Labeling?**	**Assessor’s Comments about Container Labels and Carton Labeling** (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	Requested to keep units consistent for the highest strength (i.e., display in grams)
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	

[27] Established name = [Drug] [Route of Administration] [Dosage Form]

[28] Express as “ XX mg per tablet” or “XX mg per capsule” for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Inadequate	Yes	Requested to keep units consistent for the highest strength (i.e., display in grams)
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	No	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	No	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	No	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).	N/A	Choose an item.	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5)	Adequate	No	

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
or limited space per § 201.10(i)(2)].			
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Choose an item.	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Choose an item.	
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	No	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	No	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	No	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Choose an item.	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary	N/A	Choose an item.	

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
statement is required. (USP <7>).			
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Choose an item.	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[31]	N/A	Choose an item.	
And others if space is available.	Inadequate	Yes	Revise (b) (4) to packet

Assessment of Carton Labels and Container Labeling: *Inadequate*

The deficiency to correct the established name was communicated to OND on 4-DEC-2023. Once agreed to by the applicant, labels are adequate.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

OPQ Label (Carton and Container) and Labeling (PI and Patient Information) comments were conveyed to OND 4-DEC-2023. OND has agreed to convey the above deficiencies to the Applicant on 19-JAN-2024.

The Labeling and Label of NDA 215040 is ADEQUATE from the OPQ perspective, pending the Applicant's concurrence with the Label/Labeling communication to be sent on 19-JAN-2024.

[31] USP General Notices 3.20 Indicating Conformance

Primary Labeling Assessor Name and Date:

Caroline Strasinger, PhD
CDER/OPQ/ONDP/DNDP2
01/10/2024

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Julia Pinto PhD
CDER/OPQ/ONDP
01/10/2024

Caroline Strasinger

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Date: 1/11/2024 01:23:01PM
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Julia Pinto

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Date: 1/11/2024 01:46:44PM
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/s/

HAMID R SHAFIEI
01/29/2024 01:33:48 PM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 215040
Assessment 1

Drug Product Name	Tradename (acetylcysteine)
Dosage Form	For Solution
Strength	500mg and 2.5g
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Galephar Pharmaceutical Research, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission	07/07/2022	All
General Correspondence	08/02/2022	All
General Correspondence	08/09/2022	All
Proprietary Name Request	08/16/2022	All
Labeling Package	09/22/2022	All
Response to Quality Information Request	09/30/2022	OPQ - OPMA and ONDP
Proprietary Name Request	10/07/2022	All
Response to Clinical Information Request	10/20/2022	Clinical
Response for Protocol Withdrawal	10/21/2022	Clinical
Multiple Category Submission	12/30/2022	Clinical and OPQ - ONDP
Response to Quality Information Request	01/09/2023	OPQ - OPMA
Response to Quality Information Request	02/09/2023	OPQ – OPMA and ONDP

Multiple Category Submission	02/13/2023	Clinical and OPQ – ONDP
Patent Certification	02/15/2023	All
Quality Information	03/01/2023	Clinical and OPQ

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Sharon Kelly, PhD	Lawrence Perez, PhD
Drug Product	Caroline Strasinger, PhD	Hamid Shafiei, PhD
Manufacturing	Xiumei Ruan, PhD	Christine Falabella, PhD
Microbiology	Xiumei Ruan, PhD	Christine Falabella, PhD
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Hanna Lee, Pharm D	
Application Technical Lead	Hamid Shafiei, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	Caroline Strasinger, PhD	Hamid Shafiei, PhD

NDA Executive Summary

1. Application/Product Information

NDA Number.	215040
Applicant Name	Galephar Pharmaceutical Research, Inc.
Drug Product Name	Tradename (acetylcysteine)
Dosage Form.	For solution
Proposed Strength(s)	500mg and 2.5g
Route of Administration	Oral
Maximum Daily Dose	60g
Rx/OTC Dispensed	Rx
Proposed Indication	For prevention or lessening of hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.
Drug Product Description	Tradename (acetylcysteine) for oral solution is a powder packaged as 500mg and 2.5g strengths in aluminum sachets. This drug product is indicated for prevention or lessening of hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen. Starting dose of 140mg/kg and maintenance dose 70mg/kg every 4 hours are recommended. For example, patient greater or equal 100kg are to be treated with a starting dose of 15 (six 2.5g strength) dissolved in 300mL of diet cola followed by maintenance dose every 4 hours for a maximum daily dose of 60g. For pediatric patients dosing, it is recommended to dissolve the drug product in water and administer the solution to the patients using a syringe. The active moiety acetylcysteine in the drug product is supplied as N-acetylcysteine lysine. N-acetylcysteine lysine is produced (b) (4) This API is manufactured in accordance

	with the current Good Manufacturing Practices (cGMP) requirements and tested against regulatory specification that assure the identity, strength, purity, and quality of the drug substance at release and throughout its proposed retest date. 500mg strength is composed of 948mg N-acetylcysteine lysine equivalent to 500ng of acetylcysteine and (b) (4) mg povidone (b) (4). 2.5g strength is composed of 4740mg of N-acetylcysteine lysine equivalent to 2500mg of acetylcysteine and (b) (4) mg of povidone (b) (4). (b) (4) This drug product is manufactured in accordance with the cGMP requirements and tested against regulatory specification that assure the identity, strength, purity, and quality of the drug product at release and throughout its proposed shelf-life Based on the stability data that has been submitted to the application an expiration dating period (shelf-life) of 24 months is granted to this drug product.		
Co-packaged product information	None		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 25°C – 25°C (68°F – 77°F); excursion permitted 15°C – 30°C (59°F – 86°F) [see USP Controlled Room Temperature]		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Sharon Kelly, PhD	Lawrence Perez, PhD
	Drug Product/ Labeling	Caroline Strasinger, PhD	Hamid Shafiei, PhD
	Manufacturing	Xiumei Ruan, PhD	Christine Falabella, PhD
	Biopharmaceutics	Assadollah Noory, PhD	Tapash Ghosh, PhD
	Microbiology	Xiumei Ruan, PhD	Christine Falabella, PhD

	Other (specify): Environmental Assessment	Caroline Strasinger, PhD	Hamid Shafiei, PhD
	RBPM	Hannah Lee, Pharm D	
	ATL	Hamid Shafiei, PhD	
Consults	None		

2. Final Overall Recommendation -

Complete response

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- The applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, N-acetylcysteine lysine and the drug product, Tradename (acetylcysteine) for Oral Solution, 500mg and 2.5g.
- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC PI labeling recommended changes as well as container and carton labels have been communicated to the Clinical Review Team. However, the labeling negotiation will not be pursued in this review cycle since this application will be given a complete response from the clinical perspective.
- The applicant's request for categorical exclusion from preparation of environmental assessment has been found adequate and is granted

Therefore, from the OPQ perspective this NDA is **not** ready for **approval** in its current form until the CMC labeling deficiencies and recommendations are appropriately addressed as per 21 CFR 314.125(b)(6).

The CMC PI labeling as well as container and carton labels deficiencies are captured in the Labeling Review Chapter (Chapter IV).

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Inadequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

None

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	_____	_____	Adequate Information Provided in the NDA
	III			_____	_____	Adequate Information Provided in the NDA
	IV			_____	_____	Adequate Information Provided in the NDA

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
None	--------	----------

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

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Reference ID: 5152645

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Reviewer Note: OND has made the decision to terminate labeling discussions with the applicant due to a pending CR action (as of March 8, 2023). An advice letter was sent to the referenced IND 130190 regarding the still to be conducted palatability and tolerability study. The below quality related deficiencies have been communicated to OND but not the applicant as of the date of this review.

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Inadequate	Replace with "LEGUBETI (acetylcysteine) for oral solution"
Route(s) of administration	Adequate	oral use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Inadequate	Per USP (b) (4) should be removed and just "For oral solution: 500 mg and 2.5 grams"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Inadequate	Add “of acetylcysteine”

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	Instructions included for dissolving with water and diet cola. (both vehicles supported by CMC information). Instructions to consume immediately, in its entirety within one hour.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: *“Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit”*	N/A	
If there is a USP monograph for the drug product and it contains a	N/A	

labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA H	N/A	

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Inadequate	Formatting changes requested
Strength(s) in metric system	Inadequate	Formatting changes requested
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Inadequate	Add "acetylcysteine"
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Inadequate	Formatting changes requested
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Inadequate	Remove '(b) (4)' from established name
Dosage form(s) and route(s) of administration	Inadequate	Remove (b) (4) from established name
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Inadequate	Formatting change requested
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Inadequate	an antidote for acetaminophen overdose
Chemical name, structural formula, molecular weight	Inadequate	Information for acetylcysteine lysine needs to appear in this section
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Inadequate	Information for acetylcysteine lysine needs to appear in this section

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Inadequate	Remove Powder
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Inadequate	Formatting changes requested
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Inadequate	Reword handling (e.g., (b) (4) should be solution)

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Reworded for clarity
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2], (font size and prominence)	Inadequate	Sachet name needs to increase size and differentiation Remove '(b) (4),
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Inadequate	Revise the equivalency statement without the proprietary name
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *INADEQUATE*

Revise the carton equivalency statement on the side panel for all strengths to the below:

Each sachet contains:
Acetylcysteine……..500 mg
(equivalent to 948 mg of acetylcysteine lysine)

Or

Each sachet contains:
Acetylcysteine……..2.5 grams
(equivalent to 4740 mg of acetylcysteine lysine)

QUALITY ASSESSMENT

Overall Assessment and Recommendation:

The Label and Labeling of NDA 215040 is NOT ADEQUATE. Comments and edits have been communicated to OND however will not be communicated to the Applicant due to the request for additional studies to be conducted (and pending CR action) which precludes Labeling Discussions.

This application is recommended for COMPLETE RESPONSE from the label and labeling perspective.

Primary Labeling Assessor Name and Date:

Caroline Strasinger, PhD

CDER/OPQ/ONDP/DNDP2/Branch 4

20-MAR-2023

Secondary Labeling Assessor Name and Date:

Hamid Shafiei, PhD

CDER/OPQ/ONDP/DNDP 2/Branch 4

20-Mar-2023

Caroline Strasinger

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Hamid Shafiei

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BIOPHARMACEUTICS REVIEW	
Application No.	NDA-215040-ORIG-1
Submission Classification	ORIGINAL SUBMSSION
Applicant	Galephar Pharmaceutical Research Inc.
Product Name	(b) (4) (Acetylcysteine)
Generic Name	Acetylcysteine
Dosage Form/Strengths	Powder, 500 mg, and 2.5 g
Route of Administration	Oral
Indication	Antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.
Submission Date	07/06/2022, 09/30/2022
Primary Reviewer	Assadollah Noory, Ph. D.
Secondary Reviewer	Tapash Ghosh, Ph. D.
Recommendation	**ADEQUATE**

Executive Summary

The Applicant submitted this original NDA to request approval of (b) (4) (acetylcysteine powder), indicated as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen. The listed drug (LD) MUCOMYST (Acetylcysteine solution) approved under NDA 013601 is used as the reference.

No dissolution data are provided in support of biopharmaceutics section of this NDA as the product is a powder for oral solution administration, however, to bridge the clinical and commercial formulation a biopharmaceutics review will be conducted.

An information request was sent to the Applicant regarding the solubility of acetylcysteine powder at the highest strength (15 grams) in 200 mL of all recommended solutions for administration (b) (4) water and soda pops.

In response to IR the Applicant provided the following information:

The solubility of the Acetylcysteine powder in 200 ml for administration is shown in the table below.

Table 1 - Solubility of Acetylcysteine Powder for Administration for Oral Solution

Reference ID: 5152645

Table 3 - Solubility of Acetylcysteine Powder for Administration for Oral Solution Expressed in NAC mg / ml			
	Temperature Degree in C [C°]		
	2.6	**20**	**25**
Water	248	324	346
Diet Coke	247	325	341

The solubility in water ranges from 248 mg / ml at 2.6°C up to 346 mg / ml at 25°C, and in Diet Coke ranges from 247 mg / ml at 2.6°C up to 341 mg / ml at 25°C.

Link to data:

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\\CDSESUB1\EVSPROD\nda215040\0005\m1\us\12-cover-letters\104-response-to-fda-ir.pdf

Reviewer's Assessment:

The solubility of Acetylcysteine Powder in all recommended solutions for administration exceeds the concentration of Acetylcysteine Powder resulting from (b) (4) 15 g Acetylcysteine Powder in 200 ml (75 mg/mL). Hence, there is no concern with the solubility of Acetylcysteine during administration as a powder for oral solution.

Recommendation:

The division of Biopharmaceutics finds this NDA adequate.

Reference ID: 5152645

Assadollah Noory

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Tapash Ghosh

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/s/

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