CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210660Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 210660
Assessment # 1

Drug Product Name	ELCYS (cysteine hydrochloride injection)
Dosage Form	Injection
Strength	500mg/10mL
Route of Administration	intravenous infusion after addition to TPN admixture
Rx/OTC Dispensed	Rx
Applicant	Exela Pharma Sciences, LLC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
1 - Rolling Review Designation	05/23/2017	All
28 – Revised Full NDA Submission	07/27/2018	All
29 – Response to Information Request	08/01/2018	Quality
30 – Request for Priority Designation	08/01/2018	All
31 – Response to Information Request	08/30/2018	Quality
32 – Response to Information Request	09/12/2018	Quality
33 – Response to Information Request	10/01/2018	Quality
34 – Response to Information Request	10/09/2018	Quality
35 – Response to Information Request	10/09/2018	Quality
36 – Response to Information Request	10/09/2018	Quality
37 – Response to Information Request	10/16/2018	Quality

38 – Response to Information Request	10/29/2018	Quality
39 – Response to Information Request	10/30/2018	Quality
40 – Response to Information Request	11/06/2018	Quality
41 – Response to Information Request	11/13/2018	Quality
42 – Response to Information Request	11/21/2018	Quality
43 – Amendment - Administrative	11/27/2018	All
44 – Draft Labeling	12/11/2018	All
45 – Draft Container Labels	12/14/2018	All
46 – Proprietary Name Request	12/14/2018	All
47 – Draft PI Labeling	12/17/2018	All
48 – Proprietary Name Withdrawal	12/18/2018	All
49 – Response to Information Request	01/03/2019	Quality
50 – Response to Information Request	01/15/2019	Quality
51 – Administrative	03/07/2019	All
52 – Draft PI Labeling and Container Labels	03/19/2019	All
53 – Revised PI Labeling and Container Labels	04/01/2019	All
54 – Revised PI Labeling and Container Labels	04/03/2019	All
55 – Final Draft PI Labeling	04/04/2019	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Lawrence Perez, Ph.D.	Donna Christner, Ph.D.
Drug Product	Hong Cai, Ph.D.	Moo-Jhong Rhee, Ph.D.
Manufacturing	Li Shan Hsieh, Ph.D.	Chidambaram Nallaperumal, Ph.D.
Microbiology	Jason God, Ph.D.	Denise Miller, Ph.D.
Biopharmaceutics	Rajesh Savkur, Ph.D.	Vidula Kolhatkar, Ph.D.
Regulatory Business Process Manager	Oumou Barry, MHA, MT, ASCP	

Application Technical Lead	Hamid Shafiei, Ph.D.	
Laboratory (OTR)	Nicholas Batz, Ph.D.	Connie Ruzicka, Ph.D.
Environmental	Hong Cai, Ph.D.	Moo-Jhong Rhee, Ph.D.

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QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	26-Mar-2018	Review by Lawrence Perez, Ph.D.
	III					Information provided in the NDA is sufficient
	III					Information provided in the NDA is sufficient
	III				15-Sep-2016	M. Cruz-Fisher

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

Document	Application Number	Description
New Drug Application	NDA 19523	Referenced Listed Drug

2. CONSULTS

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

U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

- The applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, purity, strength, and quality of the drug substance and drug product.
- All labels/labeling issues have been resolved.
- The Office of Process and Facility has made an overall "Acceptable" recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion of the environmental assessment is granted.

Therefore, from the OPQ perspective, this NDA is recommended for **APPROVAL** with the drug product expiration dating period of **24 months**.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Exela Pharma Sciences, LLC. has submitted this 505(b)(2) new drug application for ELCYS (cysteine hydrochloride injection), USP, 500mg/10mL (50mg/mL). Cysteine Hydrochloride Injection, 7.25%, manufactured by Hospira and approved on October 22, 1986 under NDA 19523 has been referenced as the listed drug (LD) for this application.

Hospira has discontinued marketing of the Cysteine Hydrochloride Injection and currently there is no approved drug product containing cysteine hydrochloride in the United State market. To deal with the potential drug shortage and avert the use of the unapproved cysteine hydrochloride drug products, this application was given the priority review status. The status of this application had been a rolling submission before being filed and reviewed.

ELCYS is a clear, colorless, sterile, nonpyrogenic solution containing 500mg cysteine hydrochloride equivalent to 345 mg of cysteine in 10mL (34.5mg/mL cysteine). ELCYS is a small volume parenteral (SVP) intended for use as a component of total parenteral nutrition (TPN), a large volume parenteral for intravenous infusion for the treatment of pre-term neonates, pediatric, and adult patients requiring parenteral nutrition. Prescribed amount cysteine hydrochloride is added to TPN admixtures containing other nutritional components such as amino acids, , dextrose, and other SVP additives (trace elements and electrolytes) per Prescribing Information, that are combined together to supply appropriate amounts of calories to patients through intravenous infusion. ELCYS is not to be administered alone.

ELCYS is packaged in 10-mL single-dose glass vial closed rubber stoppers and sealed with aluminum overseal, and it is supplied in cartons containing 10 vials. ELCYS formulation includes the pH adjusting agents such as hydrochloric acid and/or sodium hydroxide as needed. The referenced LD formulation did not use pH adjusting agents and it was supplied at the strength of 7.25mg/mL in a prefilled syringe. These differences were evaluated by the Biopharm review team and the Biopharm review team concluded that information provided adequately establishes the biobridge between ELCYS and the LD and therefore, there is no need for an additional in vivo bioequivalence (BE) bridging study.

From the drug product perspective, the difference in strength of the drug product compared to the LD will have no impacts on the product performance since the amount of cysteine hydrochloride that will be added to the TPN admixture will be adjusted based amount cysteine hydrochloride prescribed for each patient.

Proposed Indication(s) including Intended Patient Population	For use as a component of TPN admixture. Indicated for treatment of pre-term neonates, pediatric, and adult patients requiring PN.
Duration of Treatment	Varied. It is decided by the physician on a case-by-case basis
Maximum Daily Dose	It is adjusted based on patient weight and age.
Alternative Methods of Administration	It is added to the TPN admixture for intravenous infusion. There are no alternative methods of administration.

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, cysteine hydrochloride also referred to as L-cysteine hydrochloride is a hydrochloride salt of the natural amino acid cysteine and is a compendial active pharmaceutical ingredient with a published USP monograph. Cysteine hydrochloride for this application is supplied from (b) (4) This drug substance is produced as a monohydrate crystalline powder. It is white crystals freely soluble in water with a relative density of 1.50 (20ºC). It has a molecular weight of 175.3 g/mol and a molecular formula of $C_3H_7NO_2S.HCl.H_2O$. It is isolated as the monohydrate crystal form.

Cysteine hydrochloride supplied by (b) (4) is manufactured in accordance to cGMP and tested and released according to specification that complies to the USP monograph requirements. The proposed drug substance specification includes testing and acceptance criteria for all physical and chemical attributes essential for the determination of the identity, strength, purity and

quality of the drug substance. The specification also includes testing for additional elemental impurities required for a drug intended for use as a component of TPN admixture. All analytical methods used in testing and release of the API have been appropriately validated for their intended purpose.

Information regarding the manufacture, characterization of impurities, release and stability testing, analytical methods, specification, packaging, and retest date of cysteine hydrochloride for this new drug application is provided in DMF (b) (4) This DMF has been reviewed by the drug substance reviewer Dr. Lawrence Perez. Dr. Perez has found the information provided in DMF (b) (4) adequate to support this new drug application. Dr. Perez has recommended the approval of this application from the drug substance perspective.

Drug Product: Adequate

The drug product ELCYS (cysteine hydrochloride injection), USP, 500mg/10mL (50mg/mL cysteine hydrochloride equivalent to 34.5mg/mL cysteine) complies with compendial requirements in the current USP monograph.

Cysteine Hydrochloride Injection was previously manufactured by Hospira and approved for marketing on October 22, 1986 under NDA 19523. The marketing of Hospira's drug product that was manufactured at the strength of 7.25% has been discontinued. However, Cysteine Hydrochloride Injection manufactured by Hospira has been used as the reference listed drug (LD) for this application.

The composition of the drug product in this application is simple and contains L-cysteine hydrochloride as the active ingredient and Water for Injection and pH adjusting agents, hydrochloric acid and/or sodium hydroxide (as needed to adjust the pH of the final drug product solution to 1.0 to 2.5). The drug solution is packaged in a 10-mL (b) (4) single-dose glass vial supplied from (b) (4) closed with (b) (4) 20 mm Gray (b) (4) stopper supplied from (b) (4) as the primary container closure, capped with 20mm white, matte finish, flip-off button, aluminum (b) (4) Overseal which is also supplied from (b) (4) The use of the proposed primary container closure system is supported by extractables/leachables and stability studies. The drug product vials are packaged in cartons, each containing 10 vials.

The manufacturing process for this drug product entails (b) (4)

(b) (4)

ELCYS is tested and released according to the drug product specification that complies to the current USP monograph for cysteine hydrochloride injection and

includes testing and acceptance criteria for all physical and chemical attributes essential for the determination of the identity, strength, purity, and quality of the drug product. The drug product specification for ELCYS also include testing and acceptance criterion for aluminum content. The aluminum content for this drug product is controlled to a maximum of 120µg/L, equivalent to 0.0035µg of aluminum per mg of cysteine. The aluminum acceptance criterion in ELCYS is recommended by Pharm/Tox to ensure that infants and pediatric patient exposure to aluminum from the final TPN admixture remains at or below 5 mcg/kg/day per 21CFR201.323(e)

The applicant has provided sufficient stability data that clearly support the proposed expiration dating period of 24 months.

The information provided in the Drug Product Module of this application has been reviewed by the Drug Product Reviewer, Dr. Hong Cai. Dr. Cai has found the information provided in the drug product section of the new drug application as adequate. Dr. Cai has also found the applicant's request for categorical exclusion from the preparation of the environmental assessment to be valid. Dr. Cai has recommended the approval of this application from the drug product perspective.

Labeling: Adequate

The CMC sections of the Prescribing Information (PI) as well as the immediate container and carton labels have been reviewed by the Drug Product Reviewer, Dr. Hong Cai. Dr. Cai has found the final PI as well as immediate container and carton labels adequate and has recommended the approval of this application from labeling/labels perspective.

Manufacturing: Adequate

The manufacturing process for ELCYS (cysteine hydrochloride injection), USP, 500mg/10mL (50mg/mL) includes (b) (4)

(b) (4)

The manufacturing process has been reviewed by the Process Reviewer, Dr. Li Shan Hsieh. Dr. Hsieh has stated that the selection of the manufacturing process steps and equipment were designed based on the desired quality target product profile (QTPP) and the drug product critical quality attributes. Dr. has concluded that the manufacturing process steps are adequately controlled by the proposed in-process testing. She has found the proposed manufacturing process satisfactory

The overall assessment of the facilities involved in this application has been performed by the facilities reviewer Dr. Vidya Pai. Dr. Pai has stated that based on the inspectional history, relevant experience, and capabilities there are no risks

to the manufacturing process for this drug product. She has further expressed that a pre-approval inspection was requested for Exela Pharma Sciences, LLC. (FEI: 3008563008) the drug product manufacturing site and the outcome was acceptable. In summary Dr. Pai has recommended that all facilities involved in this application are adequate.

Biopharmaceutics: Adequate

There are some differences between the current drug product and the reference drug product. The strength of the current product is 50mg/mL while the strength of LD product was 72.5mg/mL. The formulation of the current product also contains pH adjusting agents, hydrochloric acid and/or sodium hydroxide. This drug product is packaged in glass vials while the LD product was packaged in prefilled syringes.

These differences and the applicant's request for biowaiver has been reviewed by the Biopharm Reviewer Dr. Rajesh Savkur. Dr. Savkur has stated that although the applicant request for biowaiver does not fulfill all of the requirements in 21 CFR 320.24 (b)(6), the supporting bioavailability information provided in the application is deemed adequate to establish the biobridge between this drug product and LD product. Therefore, Dr. Savkur has recommended granting biowaiver to this application.

Microbiology (if applicable): Adequate

The information regarding validity of sterilization process and process controls, package integrity, and acceptance criteria for sterility and endotoxins for ELCYS have been reviewed by the Microbiology Reviewer, Dr. Jason God. Dr. God has found that the proposed container closure is capable of adequately protecting the drug product from the external environment and maintaining the drug product sterility during the proposed drug product shelf-life.

Dr. God has also concluded that the drug product specification and validation of sterilization process comply with USP <1> Injections, <71> Sterility Test, and <85> Bacterial Endotoxins Test, as well as FDA Guidance for Industry: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

Dr. God has also concluded that the information provided regarding the design of stability testing program meets the regulatory expectations and the stability data submitted to date indicates that the drug product's microbiological quality will be maintained throughout its proposed shelf life.

In summary, Dr. God has found the microbiology section of this application as adequate.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Aluminum Content	Container closure	H	(b) (4)	Acceptable	If there are any changes to the container closure system during the product lifecycle, the leachable aluminum must be closely monitored and controlled to meet the required limit.

D. List of Deficiencies for Complete Response; None

Application Technical Lead

Hamid Shafiei, Ph.D.
Branch V/DNDP II/ONDP/OPQ

LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use (b) (4) safely and effectively. See full prescribing information for (b) (4)
Initial U.S. Approval: (b) (4)

---------- DOSAGE FORMS AND STRENGTHS ----------
(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))		
Proprietary name and established name	The product title is not presented.	**Not Satisfactory** Revise the presentation to include product title, either (b) (4) Or (b) (4) (cysteine hydrochloride injection), for intravenous use" above the initial approval date.
Dosage form, route of administration	Solution for (b) (4)	**Not Satisfactory** Revise to "Injection, for intravenous use".
Controlled drug substance symbol (if applicable)	N/A	**N/A**
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))		
Summary of the dosage form and strength	(b) (4) Injection: (b) (4) 10 mL (50 mg/mL) (b) (4) cysteine hydrochloride (b) (4) in a 10 mL single-dose vial (3).	**Not Satisfactory** Revise to: "Injection: 500 mg/10 mL (50 mg/ml) cysteine

		hydrochloride in a 10 mL single-dose vial.”

(b) (4)

2. Full Prescribing Information

Section 2 Dosage and Administration

Note: Only the following content in Section 2.3 related to storage condition of the admixture were reviewed:

(b) (4)

Item	Information Provided in NDA	Reviewer’s Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c) (12))		
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	(b) (4)	**Satisfactory*** Only the content in the left column provided in Section 2.3 of PI that related to storage condition of the admixture were reviewed for section 2 (Dosage and Administration). Although the admixture study data in CMC section does not support the stated admixture storage condition from drug product perspective, the final conclusion is based on the clinical review team recommendation. Details refer to Drug Product Review and email from the clinical reviewer Dr. Suna Seo on December 10, 2018 (Appendix I).

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))		
Available dosage forms	Not provided	**Not Satisfactory** Add the dosage form injection" after (b) (4) cysteine hydrochloride).
Strengths: in metric system	(b) (4)/10mL (50 mg/mL) (b) (4) cysteine hydrochloride (b) (4)	**Not Satisfactory** Revise to "500 mg/10 ml (50 mg/mL) cysteine hydrochloride as a clear, colorless, sterile solution in a 10 mL single-dose vial." to have consistent unit expression format (mg) and remove (b) (4)
Active moiety expression of strength with equivalence statement (if applicable)	Not provided.	**Satisfactory** Active moiety equivalence statement is not required per Label review tool in Section 3.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	(b) (4)	**Not Satisfactory** See the revision comment in the section "Strengths: in metric system".

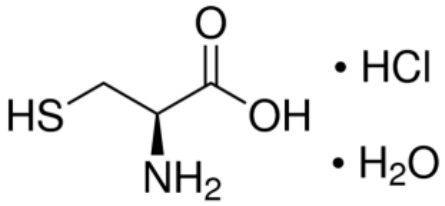
11 DESCRIPTION

(b) (4)

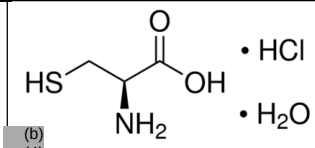
(b) (4) Sodium hydroxide and/or hydrochloric acid are used to adjust the pH. The pH range is 1.0 to 2.5. Cysteine is a sulfur-containing amino acid. (b) (4)

(b) (4)

(b) (4) L-cysteine hydrochloride monohydrate is chemically designated $C_3H_7NO_2S \cdot HCl \cdot H_2O$ (b) (4) It has the following structural formula:



Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c) (12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))		
Proprietary name and established name	(b) (4)	**Not Satisfactory** The presentation of the proprietary name and the established name is not correct. Revise to either (b) (4) or "(b) (4) (cysteine hydrochloride injection)" Also see the comment in Highlights Section for product title.
Dosage form and route of administration	(b) (4)	**Not Satisfactory** The product name, (b) (4) should be revised to (b) (4) Route of administration: for intravenous use.
Active moiety expression of strength with equivalence statement (if applicable)	Not provided.	**Not Satisfactory** Add the following statement: (b) (4)
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	(b) (4) Sodium hydroxide and/or hydrochloric acid are used to adjust the pH. The pH range is 1.0 to 2.5.	**Not Satisfactory** Revise to the following: (b) (4) Sodium hydroxide and/or hydrochloric acid are used to adjust the pH. The pH range is 1.0 to 2.5."
Statement of being sterile (if applicable)	See the statement above	**Satisfactory**
Pharmacological/ therapeutic class	Cysteine is a sulfur-containing amino acid.	**Satisfactory**

Chemical name, structural formula, molecular weight	 [redacted] cysteine hydrochloride monohydrate and is chemically designated as $C_3H_7NO_2S$ • HCl • H_2O	**Not Satisfactory** Add the chemical na [redacted] molecular weight of cysteine hydrochloride monohydrate.
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	a white crystalline powder soluble in water	**Not Satisfactory** Add the following: Cysteine aqueous solution is prone to oxidation when exposed to air, and when mixed with amino acids solutions, cysteine may convert to insoluble cystine which leads to precipitation over time.

16 HOW SUPPLIED/STORAGE AND HANDLING

[redacted] is supplied as follows:

[redacted] in 10 mL single-dose vials, packaged as 10 per carton (NDC 51754-1007-3)

Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature]. Avoid excessive heat. Protect from freezing.

Manufactured and Distributed by:

EXELA PHARMA SCIENCES

Exela Pharma Sciences, LLC
Lenoir, NC 28645

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))		
Strength of dosage form	[redacted]	**Not Satisfactory** Revise to: "[redacted] is supplied as follows: 500mg /10 mL (50 mg/mL) of cysteine hydrochloride"
Available units (e.g., bottles of 100 tablets)	[redacted] in 10 mL single-dose vials, packaged as 10 per carton	**Not Satisfactory** Revise to: "500mg /10 mL (50 mg/mL) of cysteine hydrochloride is a clear, colorless, sterile and nonpyrogenic solution in 10 mL single-dose vials, packaged as 10 per carton"
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(NDC 51754-1007-3)	**Not Satisfactory** Add the description of the formulation: "is a clear, colorless, sterile and nonpyrogenic solution."
Special handling (e.g., protect from light)	Avoid excessive heat. Protect from freezing.	**Not Satisfactory** Add the following statement for this parental SVP: *"If accidentally frozen, discard the vial."*
Storage conditions	Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature].	**Not Satisfactory** Add the admixture storage condition as the following: *"For storage of admixed solutions see Dosage and Administration (2.3)."*
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured and Distributed by: Exela Pharma Sciences, LLC Lenoir, NC 28645	**Satisfactory**

Reviewer's Assessment of Package Insert: ***Inadequate***

Review comments are made on the Prescribing Information which is based on the submission dated October 9, 2018 (SN0036).
As of this review, the Prescribing Information is not deemed satisfactory from the CMC labeling perspective (See "**List of the deficiencies**" at the end of this review).

II. Labels:

1. ***Container (vial) Label (SN0036 submitted on October 9, 2018)***

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	(b) (4)	**Not Satisfactory** Revise to either (b) (4) (cysteine hydrochloride injection)" or (b) (4) Refer to the reviewer comments in PI for the product title presentation.
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	(b) (4)	**Not Satisfactory** Revise to 500 mg/10 mL (50 mg/mL). In the side panel, the following statement should be added: Each mL contains 50 mg cysteine hydrochloride, USP (equivalent to 34.5 mg of cysteine), in water for Injection; Remove (b) (4)" from the side panel.
Net quantity of dosage form	(b) (4)	**Satisfactory**
"Rx only" displayed prominently on the main panel	Rx Only	**Satisfactory**
Lot number and expiration date	Lot Exp	**Satisfactory**
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature]. Do not freeze.	**Satisfactory** This is due to the space limitation consideration.
Bar code (21CFR 201.25)	Presented	**Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	NDC 51754-1007 (b) (4)	**Satisfactory**
Manufacturer/distributor's name	Manufactured and Distributed by: Exela Pharma Sciences, LLC, Lenoir, NC 28645 USA	**Satisfactory**

Quantitative ingredient information (injectables)	Each mL contains 50 mg (b) (4) Cysteine Hydrochloride (b) (4) May contain Sodium Hydroxide and/or Hydrochloric Acid as needed for pH adjustment. pH 1.0-2.5	**Not Satisfactory** Revise to: Each mL contains 50 mg cysteine hydrochloride, USP (equivalent to 34.5 mg of cysteine) in water for Injection; May contain Sodium Hydroxide and/or Hydrochloric Acid as need for pH adjustment. pH 1.0-2.5
Statement of being sterile (if applicable)	Not Provided	**Not Satisfactory** Add in "Sterile"
Statement of Maximum level of aluminum present at expiry of all SVP's used in the preparation of TPN solutions per 21. CFR 201.323 (c).	Contains no more than 120 mcg/L of aluminum.	**Satisfactory**

2. Carton Label (SN0036, submitted on October 9, 2018).

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	(b) (4) Side panel contains (b) (4)	**Not Satisfactory** Revise to either of these two options: (b) (4) , or (b) (4) (cysteine hydrochloride injection), USP (b) (4) should be removed from the side panel. Also refer to the reviewer comments in the container label and PI regarding the product title presentation.
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	(b) (4)	**Not Satisfactory** Revise to the following to be consistent with the unit expression as mg of the active ingredient and add the equivalence statement: 500mg /10 mL (50 mg/mL) In the side panel, add the following statement: Each mL contains 50 mg cysteine hydrochloride, USP (equivalent to 34.5 mg of cysteine) (b) (4) water for Injection;
Net quantity of dosage form	(b) (4)	**Satisfactory** Revise (b) (4) to 500 mg/10mL See the comment above.
"Rx only" displayed prominently on the main panel	Rx only	**Satisfactory**
Lot number and expiration date	LOT: EXP:	**Satisfactory**

Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 20°C – 25°C (68°F – 77°F). [see USP for Controlled Room Temperature]. (b) (4)	**Not Satisfactory** Revise to be consistent with the storage condition statement in Section #16 of PI.
Bar code (21CFR 201.25)	Provided	**Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	NDA51754-1007-3	**Satisfactory**
Manufacturer/distributor's name	EXELA pharma sciences Manufactured and Distributed by Exela Pharm Sciences, LLC Lenoir, NC 28645	**Satisfactory**
"See package insert for dosage information"	Not Provided.	**Not Satisfactory** Add the statement: "See package insert for dosage information."
Quantitative ingredient information (injectables)	Each mL contains 50 mg (b) (4) Cysteine Hydrochloride (b) (4) May contain Sodium Hydroxide and/or Hydrochloric Acid as needed for pH adjustment. pH 1.0-2.5	**Satisfactory** Refer to the comment in the Dosage strength and active moiety expression. Revise to: Each mL contains 50 mg cysteine hydrochloride, USP (equivalent to 34.5 mg of cysteine) (b) (4) water for Injection; May contain Sodium Hydroxide and/or Hydrochloric Acid as needed for pH adjustment. pH 1.0-2.5.
Statement of being sterile (if applicable)	Not Provided.	**Not Satisfactory** Add the statement of "sterile"

Reviewer's Assessment of Labels: ***Inadequate from CMC perspective***

The above review comments for the container and closure labels are based on the submission of NDA210660 on October 9, 2018 (SN0036), and as of this review, the labels for container and cartons are not deemed satisfactory from CMC perspective (see the following **List of deficiencies**).

List of Deficiencies:

A. Regarding Prescription Information:

1. *Revise the product title to one of the following format. We remind you that the presentation format should be consistent among PI, carton and container labels.*

   [redacted] *for Intravenous Use*

   Or

   [redacted] *(cysteine hydrochloride injection), for Intravenous Use*

2. *Revise the unit of the dosage strength from* [redacted] *to 500 mg/10 mL to be consistent with the expression of 50 mg/ ml. Revise the entire document accordingly.*

3. *Revise Section 3: DOSAGE FORMS AND STRENGTHS statement to the following: Injection: 500 mg/10 mL (50 mg/mL) cysteine hydrochloride as a clear, colorless, sterile solution in a 10 mL single-dose vial.*

4. *In the "Description" section (#11):*

   a) *Include the presentation of the proprietary name and established name as "*[redacted]*(cysteine hydrochloride injection)" or* [redacted] *and the route of administration as "for intravenous use." Refer to the comment #1.*

   b) *Add in the strength equivalency statement of cysteine per USP salt policy: "Each 10 mL vial contains 500 mg of cysteine hydrochloride (equivalent to 345 mg of cysteine), in* [redacted] *water for injection."*

   c) *Add "as needed" in the statement for the pH adjusters sodium hydroxide and/or hydrochloric acid: Sodium hydroxide and/or hydrochloric acid are used as needed to adjust the pH. The pH range is 1.0 to 2.5.*

   d) *Add in the statement: "The active ingredient is cysteine hydrochloride".*

   e) *Add the* molecular *weight of cysteine hydrochloride.*

   f) *Add the following important chemical property for cysteine: "Cysteine aqueous solution is prone to oxidation when exposed to air, and when mixed with amino acids solutions, cysteine may convert to insoluble cystine which leads to precipitation over time."*

5. *In the "How supplied/storage and Handling "section (#16):*

a. *See the comment #1 for the presentation of the established name.*

b. *Add in the description of the formulation: "500mg /10 mL (50 mg/mL) of cysteine hydrochloride is a clear, colorless, sterile and nonpyrogenic solution in 10 mL single-dose vials, packaged as 10 per carton (NDC 51754-1007-3)."*

c. *Add "If accidentally frozen, discard the vial." to the storage condition statement.*

d. *Add the admixture storage statement to be consistent with the statement in Section 2.3 for the storage of the admixture.*

B. Regarding Labels

For the vial label:

1. *Revise the strength expression from* (b) (4) *to "mg/mL" where is applicable. This is to maintain the consistent presentation among the labeling document.*

For the 10-vial carton label:

1. *The storage condition statement should be consistent with the statement in Section 16 of PI.*

2. *Include the admixture storage condition and the statement should be consistent with the statement in section 2.3 of PI.*

3. *Add the statement "See package insert for dosage information" to the carton label.*

For All Labels:

1. *The product title should be revised to either*

   (b) (4) *or*

   " (b) (4) *(cysteine hydrochloride injection), USP". However, it should be consistent with the presentation in the PI.*

2. *The established name is not at least half the size of the proprietary name. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).*

3. *Add "Sterile" to the container and carton labels.*

4. *Add the strength equivalency statement of cysteine per USP salt policy to the side panels of the carton and container labels.*

5. *Remove* (b) (4) *from the side panel of the carton and container labels.*

Overall Assessment and Recommendation:

From the ONDP perspective, this application is ***not*** deemed ready for approval in its present form per 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Hong Cai, Ph.D.
Drug product Reviewer
Branch V/DNDP II/ONDP/OPQ

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

I agree with Dr. Cai's assessment on the labeling and labels and concur with her recommendation that this NDA is not ready for approval as of this review.

Moo-Jhong Rhee, Ph.D.
Chief
Branch V/DNDP II/ONDP/OPQ

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Hong Cai

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Moo Jhong Rhee

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

Date: **April 4, 2018**

From: **Hong Cai, Ph.D.**
Drug Product Reviewer
Office of New Drug Products
Branch V/DNDP II

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

To: **CMC Labeling Review #1 of NDA210660**
for ELCYS (cysteine hydrochloride injection)

Subject: **Final Recommendation - APPROVAL**

At the time when Labeling Review of NDA210660 was completed on March 3, 2019, this NDA was not recommended for approval in its present form per 21 CFR 314.125(b)(8). Specifically, it was noted that labeling (Prescribing Information, container/carton) negotiations had not been completed, and in its present form, the labeling did not comply with the requirements under 21 CFR 201. The NDA for this drug product was otherwise complete and adequate from the drug product perspective.

This addendum is to document the most updated Prescribing Information of the CMC related sections: the product title in Highlights of Prescribing Information Section and Section #3, #11 and #16 in Full Prescribing Information (**Attachment-1**) and container/carton labels (**Attachment-2**), which were submitted on April 3 and 4, 2019, respectively, with all CMC labeling/label issues addressed. The labeling and labels are now acceptable from the CMC labeling perspective.

Recommendation:

The outstanding CMC label/labeling issues have been satisfactorily resolved. This application is now recommended for **approval** from the labeling/label perspective.

Hong Cai, Ph.D.
Drug Product Reviewer
Branch V, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Branch Chief
Branch V, Division II, ONDP

Attachment-1:

Sections reviewed in the FULL PRESCRIBING INFORMATION: (submitted on April 4, 2019, SN0055)

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

ELCYS (cysteine hydrochloride injection), USP for intravenous use
Initial U.S. Approval: 1971

---------- **DOSAGE FORMS AND STRENGTHS** ----------
Injection: 500 mg/10 mL (50 mg/mL) cysteine hydrochloride in a 10 mL single-dose vial. (3)

Contents in Full Prescribing Information: Contents

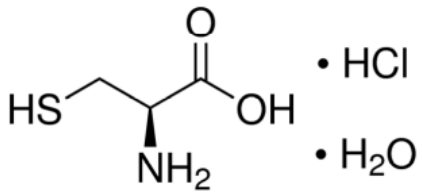
3 DOSAGE FORMS AND STRENGTHS

Injection: 500 mg/10 mL (50 mg/mL) cysteine hydrochloride as a clear, colorless, sterile solution in a 10 mL single-dose vial.

11 DESCRIPTION

ELCYS (cysteine hydrochloride injection) is a sterile, nonpyrogenic solution for intravenous use. Each 10 mL of ELCYS contains 500 mg of cysteine hydrochloride (equivalent to 345 mg of cysteine) in water for injection. Sodium hydroxide and/or hydrochloric acid are used as needed to adjust the pH. The pH range is 1.0 to 2.5.

The active ingredient is cysteine hydrochloride. Cysteine is a sulfur-containing amino acid. The chemical name of cysteine hydrochloride is L-cysteine hydrochloride monohydrate and is chemically designated as $C_3H_7NO_2S \cdot HCl \cdot H_2O$ having a molecular weight of 175.63. Cysteine hydrochloride is a white crystalline powder soluble in water. Cysteine aqueous solution is prone to oxidation when exposed to air, and when mixed with amino acids solutions, cysteine may convert to insoluble cystine which leads to precipitation over time. It has the following structural formula:



ELCYS contains no more than 120 mcg/L of aluminum.

16 HOW SUPPLIED/STORAGE AND HANDLING

ELCYS is supplied as follows:

500 mg/10 mL (50 mg/mL) of cysteine hydrochloride is a clear, colorless, sterile and nonpyrogenic solution in 10 mL single-dose vials (51754-1007-1), packaged as 10 per carton (NDC 51754-1007-3)

Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature]. Avoid excessive heat. Protect from freezing. If accidentally frozen, discard the vial.

For storage of admixed solution see *Dosage and Administration (2.3).*

Manufactured and Distributed by:

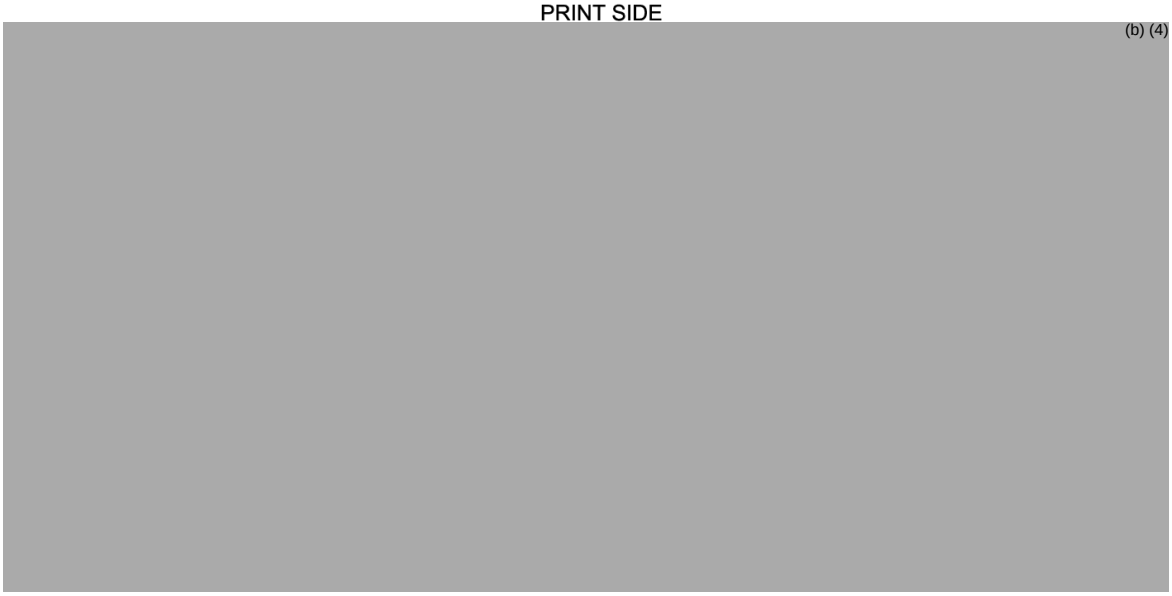
Exela Pharma Sciences, LLC
Lenoir, NC 28645

Attachment-2 (submitted on April 3, 2019, SN0054):

Carton Labels for ELCYS (cysteine hydrochloride injection), USP 500 mg/10 mL (50 mg/mL)

ELCYS Injection, USP
Carton
Round 9: 04-03-19 by (b) (4)

EXELA PHARMA SCIENCES, LLC
CC11588A
PRINT SIDE



Container (Vial) Label:

ELCYS Injection, USP
Vial

Round 9: 4-03-19 by (b) (4)

Hong Cai

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Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
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BIOPHARMACEUTICS

IQA Review Guide Reference

Product Background:

NDA:210660

Drug Product Name / Strength: L-Cysteine HCl Injection, USP, 50 mg/mL

Route of Administration: Intravenous (IV)

Indication: TPN (Total Parenteral Nutrition)

Applicant Name: Exela Pharma Sciences, LLC.

Review Summary:

The proposed drug product, L-Cysteine Hydrochloride Injection, USP is a clear solution intended for administration by intravenous (IV) injection for TPN (total parenteral nutrition). The reference listed drug (LD) is Hospira Inc.'s Cysteine Hydrochloride Injection, USP (NDA No. 019523), which was approved on 10/22/1986, but discontinued on 06/16/2006 for reasons other than safety and efficacy.

NDA 210660 that was submitted on 03/03/17 under 505(b)(2), was submitted to the Agency on a rolling basis. On 07/21/18, it was designated as a priority review (6 months). The review clock started on 07/27/18 and the PDUFA goal date is 01/27/19.

The composition of the Test and Reference drug products is shown in Table 1. The proposed test drug product has the same active ingredient, dosage form, route of administration, preparation for administration, and indications as the reference LD, except that the active ingredient concentration in the reference drug product is 72.5 mg/mL whereas the proposed Cysteine Hydrochloride Injection, USP is 50 mg/mL.

Table 1. A comparison of Exela's L-Cysteine Hydrochloride Injection, USP with the RLD product

Parameter	Exela's L-Cysteine Hydrochloride Injection, USP	RLD Product[1]
L-Cysteine Hydrochloride, Monohydrate, USP	50 mg/mL	72.5 mg/mL
Sodium Hydroxide, NF and/or Hydrochloric Acid, NF	To adjust pH (product pH: 1.0 to 2.5)	(b) (4)
Water for Injection, USP	(b) (4)	
Presentation	10 mL single use glass vial	10 mL additive syringe glass barrel
Preparation for Administration (dilution/mixing procedure)	Same as RLD	As per the package insert
Concentration of Cysteine Hydrochloride in the Administration Solution	Same as RLD	As per the package insert
Infusion Rate	Same as RLD	As per the package insert

[1]Information regarding Hospira Inc.'s Cysteine Hydrochloride Injection, USP was obtained from the package insert, vial label, and carton label.

(b) (4)

L-Cysteine Hydrochloride Injection is required to be administered only upon dilution and based on body weight and/or other requirements of the patient. The Applicant submitted a biowaiver request according to 21CFR320.22 (b)(1). However, the biowaiver request could not be applied to the proposed drug product because it is not the same as the reference listed drug (LD) due to difference in strength. Furthermore, the LD is supplied as a 10 mL additive syringe glass barrel whereas the proposed drug product is supplied in a 10 mL single use glass vial.

The Reviewer's assessment to the original review in the submission: NDA 210660 0000 (1) ORIG-1 dated 03/03/2017, is listed below:

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: ***{Adequate/Inadequate} Not Applicable***

{Assess method development, method robustness, and criteria; modeling approach}

This is an injectable product; therefore, dissolution assessment is not needed.

Biowaiver Request

Reviewer's Assessment: ***Adequate***

Although the criteria for a biowaiver under 21 CFR 320.22(b)(1) is not fully met, based on 21 CFR 320.24(b)(6), the FDA can rely on any other approach deemed adequate by FDA to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products.

1. Justification of the difference in drug strength

To evaluate the biowaiver request, it is important to know whether the difference in drug concentration would affect the drug absorption and in vivo performance.

The RLD, 7.25% Cysteine Hydrochloride Injection, USP is indicated for use as an additive to amino acid solutions to meet nutritional requirements of newborn infants requiring total parenteral nutrition (TPN) and of adult and pediatric patients with severe liver disease who may have impaired enzymatic processes and require TPN. It can also be added to amino acids solutions to provide a more complete profile of amino acids for protein synthesis.

The RLD, 7.25% cysteine HCl injection (0.725 g as the monohydrate, MW is 175.63 g/mol), USP is supplied as a 10 mL solution each providing 0.5 g of cysteine (MW is 121.16 g/mol) and 4.13 mEq of chloride in water for injection, USP. In clinical practice, it would be diluted by mixing with amino acids solution to provide cysteine at approximately 1.5% of the total amino acids being supplied. For addition to amino acids solutions that are intended for use in adults, a dosage of 5 mg of cysteine per gram of amino acids can be used.

For example, for RLD, an infant receiving amino acids solutions at 2.5 g/kg/day should be provided 37.5 mg (1.5% (1.5% of the total amino acids) x 2.5 g /kg/day) of cysteine or 0.75 mL /kg/day of cysteine (0.725g of cysteine monohydrate equals to 0.5 g of cysteine, and thus 37.5 mg/50 mg=0.75 mL) or 0.75 mL/kg/day of 7.25% Cysteine Hydrochloride Injection, USP. Then these amino acids admixtures would be further diluted with appropriate caloric substrates calculated to supply the patient with adequate energy.

The proposed drug product, Cysteine Hydrochloride Injection, USP is a sterile, nonpyrogenic solution containing 50 mg of L-Cysteine Hydrochloride Monohydrate in 1 mL of water for injection, and it is supplied in a 10 mL single use glass vial. As stated in the proposed label, the proposed drug product would be diluted similarly as RLD with amino acids solution to provide L-cysteine at 1.5% of the total amino acids being supplied. Due to the difference in the proposed dose strength, the volume would be adjusted accordingly. For example, an infant receiving amino acids solutions at 2.5 g/kg/day should be provided 37.5 mg/kg/day of cysteine (1.5% x 2.5g = 37.5 mg) or 1.1 mL/kg/day of L-Cysteine Hydrochloride Injection, USP (50 mg of cysteine HCl monohydrate equals to 34.5 mg of L-cysteine, and thus, 37.5 mg /34.5 mg of L-cysteine = 1.1 mL; i.e, 1.1 mL is needed for the proposed drug product vs. 0.75 mL for RLD to deliver the same dose).

Therefore, for both RLD and the test drug product, as described in above, only a small amount of L-Cysteine HCl injection would be needed in clinical practice to mix with relative large amount of amino acid solutions.

For an infant receiving 2.5 g/kg/day: 0.75mL of RLD or 1.1 mL of the test drug product mixed with 22 mL of Novamine (11.4% amino acids); or for adult receiving 5 mg of cysteine per gram of amino acids (0.5% of total amino acids), 6 mL of RLD would be mixed with

500 mL of Novamine solution to provide a final concentration of 60 mg L-cysteine/100 mL of amino acid solutions; or 7.3 mL of the test drug product would be mixed with 500 mL of Crystalline Amino Acid Injection 10% to provide a final concentration of 50 mg L-cysteine /100 mL of amino acids solution). Since this is a clear solution, and as a result of dilution before injection, the difference in the initial drug strength would not likely affect drug absorption and thus the different in initial drug strength of 72.5 mg/mL (Reference) and 50 mg/mL (Test) is not critical. It is, however, critical that to constitute/obtain the same final amount to be given to the patients is important.

The Applicant's justification is acceptable.

2. Physical and chemical comparison

As specified in the current USP monograph for L-Cysteine Hydrochloride Injection, USP, the pH specification for L-Cysteine Hydrochloride Injection, USP is "1.0 - 2.5". The Applicant applied the same specifications for the proposed drug product.

However, it is noticed that the osmolality testing results of the three (3) submission stability exhibit batches were 644, 648, and 649 mOsm/kg, and the Applicant proposed a release osmolality specification of (b) (4) mOsm/kg. Therefore, the proposed drug product is hypertonic, which might pose safety risk. After consulting with the medical team, the following IR was conveyed to the Applicant on 06/23/2017:

An IR was previously submitted to the Applicant:

1. **Since your proposed drug product is hypertonic (osmolality ~600 mOsm/kg), this may pose safety concerns when added or diluted in hypertonic TPN, especially for peripheral IV administration. Indicate what will be the final osmolality of the diluted solution.**

The Applicant response to the IR is shown below and was deemed acceptable and adequate:

The Applicant justified the safety of the hypertonic based on literature. The osmolality data cited in the literature stated that TPN solutions were tolerated at an osmolality range of 860 to 1700 mOsm/L, and it is best to be infused at a rate of around 100 mOsm/hr. The report recommends osmolality of about 900 mOsm/L for peripheral administration (Boullata, J et al., A.S.P.E.N. Clinical Guidelines: Parenteral Nutrition Ordering, Order Review, Compounding, Labeling, and Dispensing, J Par and Ent Nut, 38 (3): 334-377, 2014.). The osmolality of the proposed drug product falls within range reported in the literatures above, thus the safety risk of this high osmolality issue would be considered low. The Applicant's justification is reviewed and found acceptable.

The RLD product was available as a 10 mL additive syringe glass barrel while Exela's drug product is formulated as 10 mL USP (b) (4) Glass Vial. The Applicant performed solution compatibility studies which indicated that the different container closure system would not be expected to affect the safety or efficacy of the proposed drug product. The acceptance of the container closure system would be reviewed by the drug product reviewer. During the review, the Applicant is requesting the permission to amend the

current NDA filing with the (b) (4) size product. As the concentration keeps the same, it is unlikely that the different size container would affect the drug absorption. The drug product reviewer will also make a final decision regarding this NDA amendment**.**

Upon review of the above information, the difference in concentration and relative high osmolality do not affect the safety and/or efficacy. Based on the 21 CFR 320.24(b)(6) regulation, from Biopharmaceutics perspective, we consider the bridge (bioavailability/bioequivalence) between the proposed drug product and the listed drug product has been established.

FDA deemed adequate the information supporting the relative bioavailability to establish a bridge to the Agency's finding of safety and effectiveness for the listed drug. Therefore, from the scientific point of view, the bioavailability of drug product is acceptable and additional in vivo bioequivalence (BE) bridging study is not needed.

Admixture Studies:
The test product and the RLD are concentrated solutions intended for administration only after further dilution and admixture. Per Agency's request, the Applicant has prepared three admixtures of the test product in Travasol 10% (Amino Acid) at 0.75 mg/mL, 2.25 mg/mL and 4 mg/mL and with Travasol 10% (Amino Acid) and dextrose injection, and has conducted evaluations of physical appearance, pH, assay, visual particulate matter, particulate matter, and osmolality at various time points up to forty-eight hours at controlled room temperature (20 ºC - 25 ºC) and up to twenty-four hours under refrigerated conditions (2 ºC - 8 ºC).

The Applicant submitted the in vitro admixture study results and reported that the test product is stable in the admixtures in terms of physical appearance, pH, assay, visual particulate matter, particulate matter, and osmolality. However, there was a lack of assay stability in the admixture samples containing dextrose. The Applicant has attributed the rapid change in assay values of admixtures to the formation of the adduct (b) (4) which occurs in TPN solutions containing L-cysteine and Glucose and has stated that it does represent degradation of L-Cysteine via oxidative pathways. This data/report will be further reviewed by the DS/DP reviewer.

List Submissions being reviewed (table):

NDA-210660-ORIG-1/Sequence 0026 dated 05/02/2018
NDA-210660-ORIG-1/Sequence 0028 dated 07/28/2018

Concise Description Outstanding Issues Remaining: None

In the current submission, the Applicant has not submitted any new Biopharmaceutics data to review. The current submission contains only CMC information, and this will be reviewed by the DS or the DP reviewer.

The request for the biowaiver was granted in the previous cycle of review. From a Biopharmaceutics perspective, the current submission is deemed adequate and the conclusions regarding the granting of the biowaiver sustain.

Biopharmaceutics Conclusions:
In consistence with 21 CFR 320.24 (b)(6), FDA deemed the information supporting the relative bioavailability of the proposed drug product to the listed drug to be adequate, and a ***biobridge*** has been established to the Agency's finding of safety and effectiveness for the listed drug, Thus, an additional in vivo bioequivalence (BE) bridging study is not needed.

List of Deficiencies: None

From Biopharmaceutics perspective, NDA 210660 is recommended for approval.

Primary Biopharmaceutics Reviewer Name and Date:

Rajesh Savkur, Ph.D. 8/15/2018

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

Tien-Mien Chen, Ph.D.
Acting Biopharm. Lead I concur. 11/20/18
DB/ONDP/OPQ

Tien Mien Chen

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Date: 11/20/2018 03:15:37PM
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Comments: I concur. 11/20/18

Rajesh Savkur

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MICROBIOLOGY

Product Background: The drug product is a (b) (4) sterile solution indicated for the treatment of newborns requiring total parental nutrition (TPN) and in adult patients with severe liver disease and impaired enzymatic processes requiring TPN.

NDA: 210660

Drug Product Name / Strength: L-cysteine HCL Injection, USP / 50 mg/ml

Route of Administration: IV

Applicant Name: Exela Pharma Sciences, LLC

Manufacturing Site:
Exela Pharma Sciences, LLC
1245 Blowing Rock Blvd.
Lenoir, NC 28645

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Review Summary: The drug product is (b) (4). This review covers the validation of (b) (4) of related components.

List Submissions Being Reviewed:
05/23/2017
08/28/2017
09/21/17
10/20/17
02/01/2018
10/9/2018
10/29/2018
11/6/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: There were six information requests sent. The first was issued by the Agency on 31 July 2017, and the applicant responded on 28 August 2017. The second IR was issued on 4 October, and a response was received on 20 October 2017. The third IR was issued on 1 December 2017, and the applicant's response was received 1

February 2018. The fourth IR was issued on 26 September 2018, and the applicant's response was received 9 October 2018. The fifth IR was issued on 15 October 2018 and the applicant's response was received 29 October 2018. The sixth IR was issued on 2 November 2018 and the applicant's response was received 6 November 2018.

Concise Description Outstanding Issues Remaining: (None)

Supporting Documents:
DMF (b) (4) was reviewed by the Division of Microbiology Assessment on 3 February 2017 (D11648M33R01.doc) and found adequate.

DMF (b) (4) was reviewed by M. Cruz-Fisher on 15 September 2016 (D23116MRo2R01.doc) and found adequate.
List Number of Comparability Protocols (ANDA only): N/A

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** Clear, colorless, sterile, non-pyrogenic solution for IV injection, supplied in a 10 mL, single dose vial.

- **Drug product composition –**

Table 1: Composition of L-Cysteine HCl Injection

Component	Quality Standard	Function	Quantity per vial (10 mL Vial)
L-Cysteine Hydrochloride Monohydrate, USP	USP	Drug Substance	500 mg
Sodium Hydroxide*	NF	pH Adjuster	q.s. to adjust the pH to about (b) (4)
Hydrochloric Acid*	NF	pH Adjuster	q.s. to adjust the pH to about (b) (4)
Water for Injection	USP	(b) (4)	(b) (4)

Table 1 was reproduced from the applicant's "description-and-composition.pdf," page 3/3, located in Module 3.2.P.1

- **Description of container closure system –** 10 mL, clear, (b) (4) USP, glass vials, sealed with 20 mm, gray stoppers and aluminum overseals.

  Reviewer note: There was some confusion about whether or not the sponsor intended to (b) (4) There were several IRs issued over this and the sponsor confirmed in IR #6 that the (b) (4) will not be included at this time. See section P.2.5 Container/Closure and Package Integrity section.

P.2 Pharmaceutical Development

(b) (4)

Hamid Shafiei

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