Doc Code: PA.
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 01/31/2018. OMB 0651-0035
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

# POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

| Application Number | Filing Date |
|---|---|
| | |

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 00826

**OR**

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

**Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:**

☑ The address associated with the above-mentioned Customer Number

**OR**

☐ The address associated with Customer Number:

**OR**

| | | | | | |
|---|---|---|---|---|---|
| ☐ Firm or Individual Name | | | | | |
| Address | | | | | |
| City | | State | | Zip | |
| Country | | | | | |
| Telephone | | Email | | | |

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Exela Pharma Sciences, LLC

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

**SIGNATURE of Applicant for Patent**

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

| | | | |
|---|---|---|---|
| Signature | | Date (Optional) | |
| Name | MANESH KANERU | | |
| Title | PRESIDENT | | |

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ Total of 1 forms are submitted.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

# ELECTRONIC PAYMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| 18/067,287 | 12/16/2022 03:33:16 PM ET | 066859/589619 |

## Title of Invention

STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 9793 | FILED BY | Raquel West |
| PATENT CENTER # | 61312420 | AUTHORIZED BY | Bryan Skelton |
| CUSTOMER # | 826 | FILING DATE | - |
| CORRESPONDENCE ADDRESS | - | FIRST NAMED INVENTOR | John Maloney |

## Payment Information

| PAYMENT METHOD | PAYMENT TRANSACTION ID | PAYMENT AUTHORIZED BY |
|---|---|---|
| DA / 160605 | E2022BFF33533146 | Raquel West |

| PRE-AUTHORIZED ACCOUNT | PRE-AUTHORIZED CATEGORY |
|---|---|
| 160605 | 37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges) |

| FEE CODE | DESCRIPTION | ITEM PRICE($) | QUANTITY | ITEM TOTAL($) |
|---|---|---|---|---|
| 1011 | BASIC FILING FEE - UTILITY (PAPER FILING ALSO REQUIRES NON-ELECTRONIC FILING FEE UNDER 1.16(T)) | 320.00 | 1 | 320.00 |
| 1311 | PATENT APPL. EXAMINATION FEE | 800.00 | 1 | 800.00 |
| 1202 | EACH CLAIM IN EXCESS OF 20 | 100.00 | 10 | 1000.00 |
| 1830 | PROCESSING FEE, EXCEPT IN PROVISIONAL APPLICATIONS | 140.00 | 1 | 140.00 |

| | | | | |
|---|---|---|---|---|
| 1817 | REQUEST FOR PRIORITIZED EXAMINATION | 4200.00 | 1 | 4200.00 |
| 1111 | UTILITY PATENT APPL. SEARCH FEE | 700.00 | 1 | 700.00 |
| | | | **TOTAL AMOUNT:** | **$7,160.00** |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/01 (06-12)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


# DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

| Title of Invention | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE |
|---|---|

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 16/248,460

filed on January 15, 2019.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

## WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: John Maloney Date (Optional): 1/21/19

Signature: John Maloney

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


# DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

| | |
|---|---|
| **Title of Invention** | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE |

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 16/248,460 filed on January 15, 2019.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: Aruna Koganti Date (Optional): 01/21/2019

Signature: K. Aruna Reddy

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


# DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

| | |
|---|---|
| **Title of Invention** | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE |

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 16/248,460 filed on January 15, 2019.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: Phanesh Koneru Date (Optional):

Signature:

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **18/067,287** | **12/16/2022 03:33:16 PM ET** | **066859/589619** |

## Title of Invention

STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 9793 | FILED BY | Raquel West |
| PATENT CENTER # | 61312420 | FILING DATE | - |
| CUSTOMER # | 826 | FIRST NAMED INVENTOR | John Maloney |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Bryan Skelton |

## Documents

**TOTAL DOCUMENTS: 11**

| DOCUMENT | | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|---|
| 589619_ADS.pdf | | 9 | Application Data Sheet | 2174 KB |
| 589619_TRACK1.pdf | | 2 | Track One Request | 79 KB |
| 589619_PAM.pdf | | 3 | - | 109 KB |
| 589619_PAM-A.PE.pdf | (1-1) | 1 | Preliminary Amendment | 103 KB |
| 589619_PAM-SPEC.pdf | (2-2) | 1 | Specification | 103 KB |
| 589619_PAM-REM.pdf | (3-3) | 1 | Applicant Arguments/Remarks Made in an Amendment | 103 KB |
| 589619_DWGS.pdf | | 5 | Drawings-only black and white | 125 KB |

| | | | | |
|---|---|---|---|---|
| | | | line drawings | |
| 589619_DEC.pdf | | 3 | Oath or Declaration filed | 354 KB |
| 589619_POA.pdf | | 1 | Change of Address | 176 KB |
| 589619_TRACK1con.pdf | | 94 | - | 621 KB |
| 589619_TRACK1con-SPEC.pdf | (1-87) | 87 | Specification | 605 KB |
| 589619_TRACK1con-CLM.pdf | (88-93) | 6 | Claims | 74 KB |
| 589619_TRACK1con-ABST.pdf | (94-94) | 1 | Abstract | 65 KB |

## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| 589619_ADS.pdf | E4003D8C624162AC4F7282115F9C504A63331A63EBF611E5D7054E0F53499AD5AEDA927FD3B40F18BE1BEA415FCB7510B8221A36ECFFEBD4AAC2A864C934328F |
| 589619_TRACK1.pdf | 96F1E639296B2C2EBFD88E13ACDD8C6956F17B63891736C66FBDC862B9F87B699CA24FCAAF08AC535B076F0AFB004D3A948313C577F957FAFF972CF8C3677A0C |
| 589619_PAM.pdf | 52C75D16CED8AFFAEB42383D7CAEF7C6227071C6E5B9E8733B5A182A0E30E77D43AE18B3F592DC942142DDC344AFFDADA5840CC4683FBA0C49E9CF5616FE2417 |
| 589619_PAM-A.PE.pdf | DF64690370515F3DB3957E0C66AB49E302247765FD20B3FACC4939025BA4ABD73E391066A75A15BC9B462375EBF76BF818DFF6D48056574B943F43D8C36B01BE |
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| 589619_DWGS.pdf | 9D0DECC08938C9E9E5A563DA4B84D4506E7013E22DCBE0F091BAA1FFB86A22D60D6FB4D48CD610968A95BE68D66E7E4F107F73A251470CBE8FE87DE791D6FAD4 |
| 589619_DEC.pdf | CB88A94202823202CE1B18DAFEDE1C02925C64C0CAE3321DB92AB6B10114D7462B1520D39A02DCA4119A605C1FB3307C7F0A70417F26C7AA3AF6CEE475E6A8D4 |
| 589619_POA.pdf | 140A4553D331D9A1771A89C2E22AC8E21AA6F3BCF52007A3B97D87404A686CCE004A80C81A9D924006D8F567C6268B4A469CD86EA87DE4C2D7A454D39EF4090F |
| 589619_TRACK1con.pdf | 91B16CC586F3A913B29999EE2A453FACF6554E115E67E4FDADEF3BC6C999AB0D3D6A46EC0C18F9ACBB61FEE127D54933F5B1908E6EAC7EF60934D7E23A33B443 |
| 589619_TRACK1con-SPEC.pdf | E677A0ADBE4B3BDEA953846C431C76128527FE78FEC3C1A5647F347F68E587FC1954CD0DD17978CC57A9C6F1145A97FA86958507212D932508412AE69BAE6A8F |
| 589619_TRACK1con-CLM.pdf | 4B30EBBC80C04D23BEA561E66AE746893FF2357625B6214AB3DC345BB34F260C95CB7AEFB04B58FCCDE9595B82EF1319358CA33DD8F843CFAAEF724329DBB9F7 |
| 589619_TRACK1con-ABST.pdf | 7F0378FA388208D91FEEFC3D6692B3585FF34AE0AEDDCF2417D3CC70559AF51CE4DB5C4938B6A576CB6DF93121E9B3E0DAA61F116BB96553D4F3E6151379E013 |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d)

and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

**Doc Code: TRACK1.REQ**
**Document Description: TrackOne Request**

PTO/AIA/424 (04-14)

## CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

| | | | |
|---|---|---|---|
| First Named Inventor: | John Maloney | Nonprovisional Application Number (if known): | TBA |
| Title of Invention: | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE | | |

**APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.**

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

**I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

**II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

| | |
|---|---|
| Signature /Bryan L. Skelton/ | Date December 16, 2022 |
| Name (Print/Typed) Bryan L. Skelton | Practitioner Registration Number 50893 |

***Note:*** *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

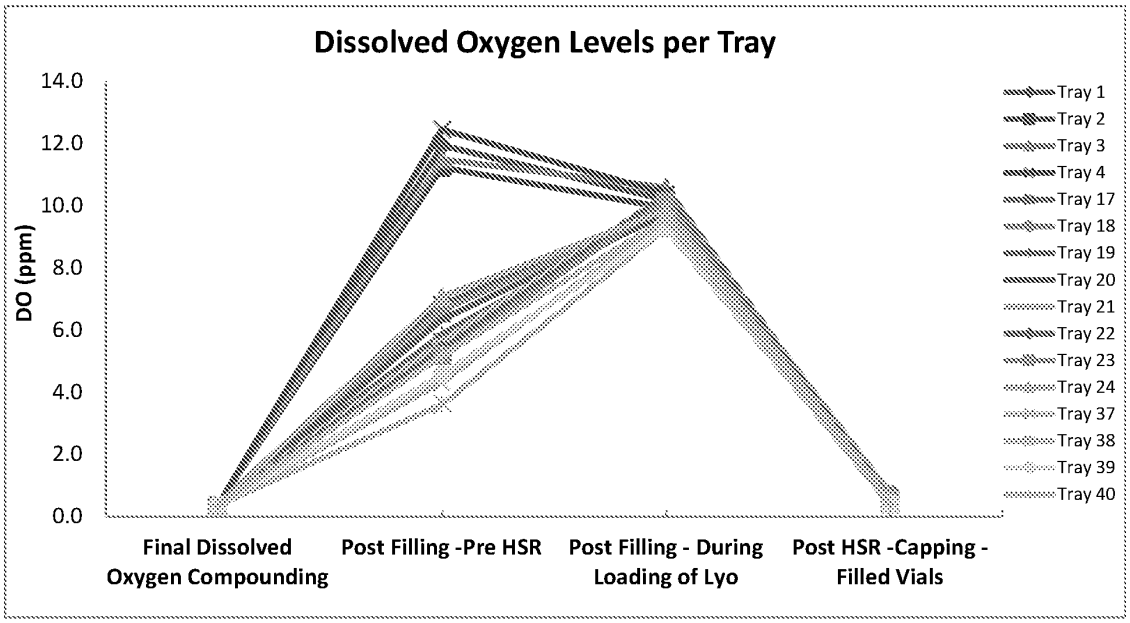
☑ *Total of 1 forms are submitted.

## Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.


Dissolved Oxygen Levels per Tray
DO (ppm)
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
Final Dissolved Oxygen Compounding
Post Filling -Pre HSR
Post Filling - During Loading of Lyo
Post HSR -Capping - Filled Vials
Tray 1
Tray 2
Tray 3
Tray 4
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Tray 40

*FIG. 1*

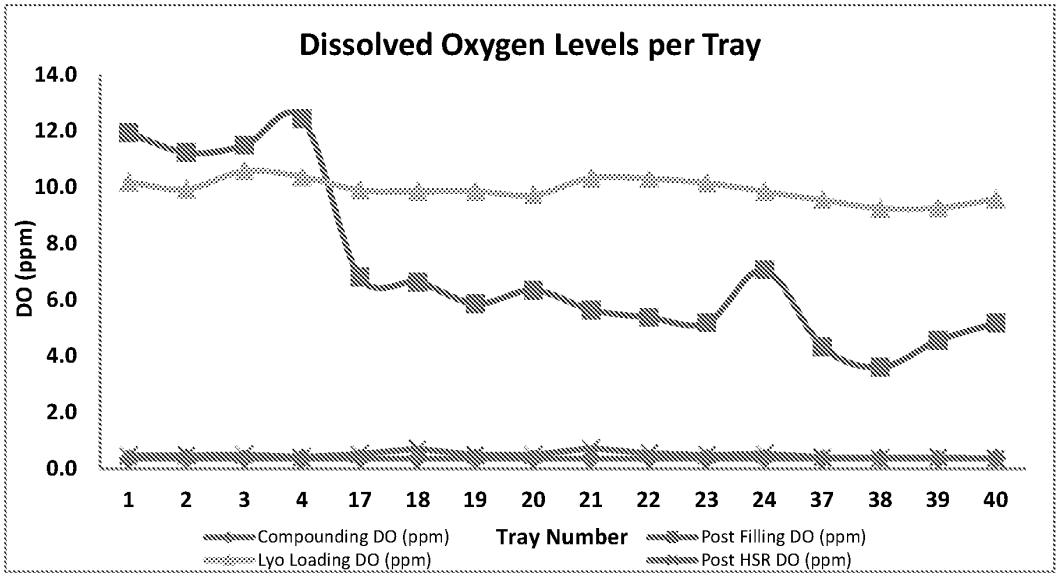
Dissolved Oxygen Levels per Tray
DO (ppm)
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
1
2
3
4
17
18
19
20
21
22
23
24
37
38
39
40
Tray Number
Compounding DO (ppm)
Lyo Loading DO (ppm)
Post Filling DO (ppm)
Post HSR DO (ppm)

*FIG. 2*

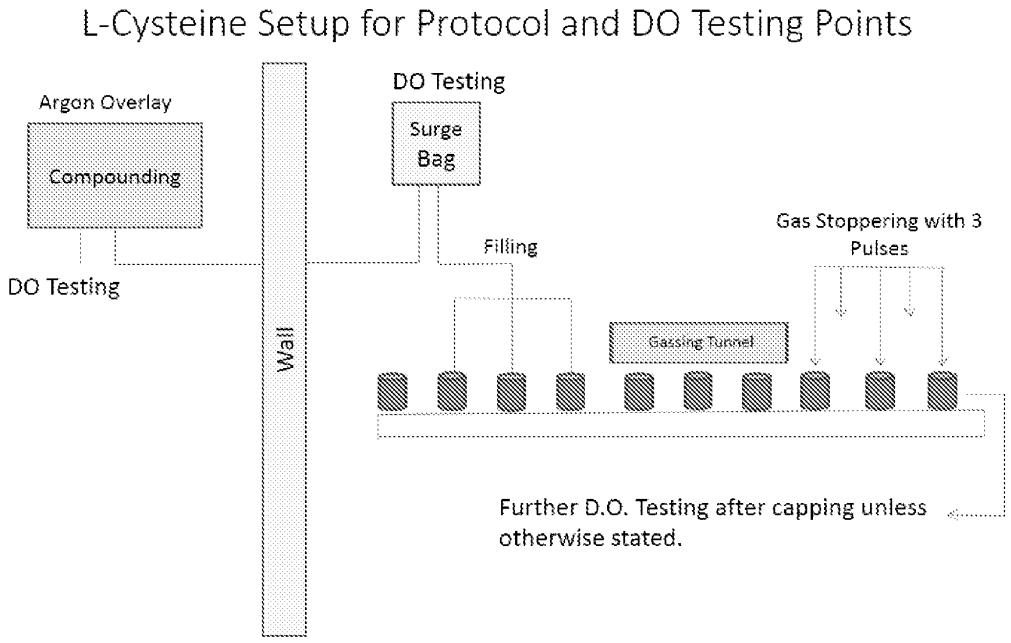
L-Cysteine Setup for Protocol and DO Testing Points
Argon Overlay
Compounding
DO Testing
DO Testing
Surge
Bag
Filling
Wall
Gas Stoppering with 3
Pulses
Gassing Tunnel
Further D.O. Testing after capping unless
otherwise stated.

***FIG. 3***

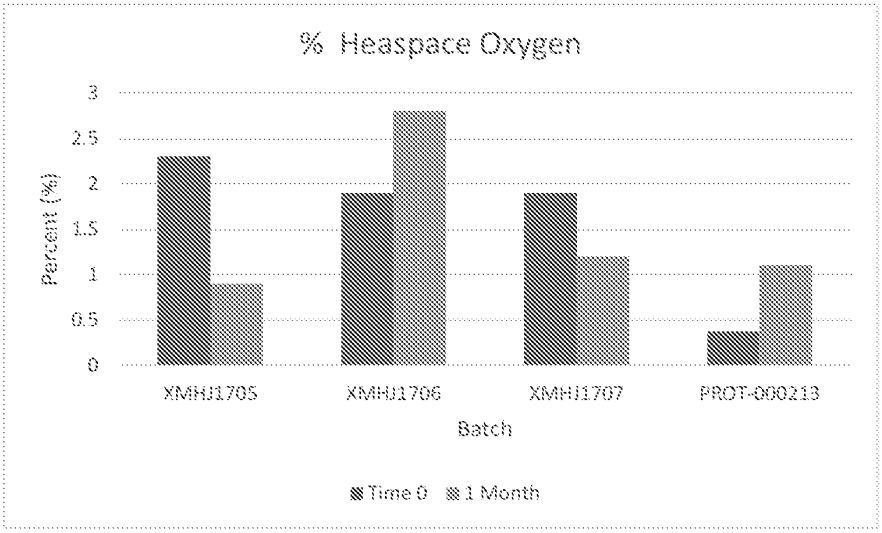
% Heaspace Oxygen
Percent (%)
3
2.5
2
1.5
1
0.5
0
XMHJ1705
XMHJ1706
XMHJ1707
PROT-000213
Batch
Time 0
1 Month

*FIG. 4*

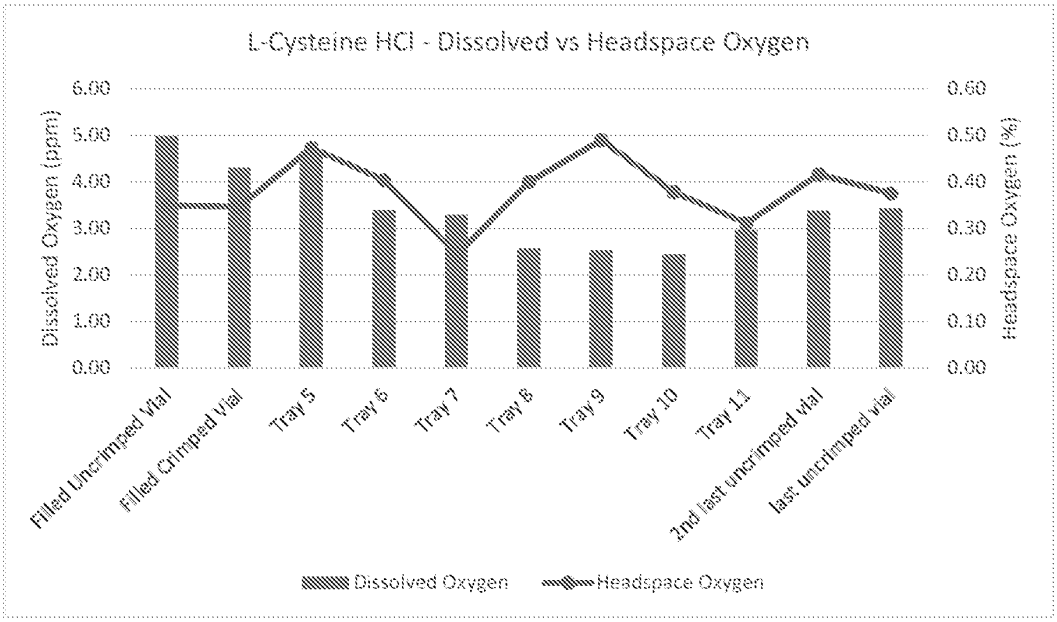
L-Cysteine HCl - Dissolved vs Headspace Oxygen
Dissolved Oxygen (ppm)
Headspace Oxygen (%)
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Filled Uncrimped Vial
Filled Crimped Vial
Tray 5
Tray 6
Tray 7
Tray 8
Tray 9
Tray 10
Tray 11
2nd last uncrimped vial
last uncrimped vial
Dissolved Oxygen
Headspace Oxygen

*FIG. 5*

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | |
|---|---|---|
| Appl. No.: | Unassigned | Confirmation No.: Unassigned |
| Applicant(s): | EXELA PHARMA SCIENCES, LLC | |
| Filing Date: | Herewith | |
| Art Unit: | Unassigned | |
| Examiner: | Unassigned | |
| Title: | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE | |
| Docket No.: | 066859/589619 | |
| Customer No.: | 826 | |

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**PRELIMINARY AMENDMENT**

Sir:

Please enter this Preliminary Amendment before calculating the claim fee and amend the above-identified application as follows:

**Amendments to the Specification** begin on page **2** of this paper.

**Remarks** begin on page **3** of this paper.

**Amendments to the Specification:**

Please amend the first paragraph of the specification as follows:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application no. 17/950,964 filed September 22, 2022, which is a continuation of U.S. application no. 17/188,922 filed March 1, 2021, now U.S. patent no. 11,510,942, which is a continuation of U.S. application no. 16/746,028 filed January 17, 2020, now U.S. patent no. 10,933,089, which is a continuation of U.S. application no. 16/665,702 filed October 28, 2019, now U.S. patent no. 10,583,155, which is a continuation of 16/248,460 filed January 15, 2019, now U.S. patent no. 10,478,453, which are hereby incorporated by reference in their entirety.

## REMARKS

The specification has been amended to update priority the information for this application.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 919-862-2241.

Respectfully submitted,

/Bryan L. Skelton/

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**ELECTRONICALLY FILED USING THE EFS-WEB ELECTRONIC FILING SYSTEM OF THE UNITED STATES PATENT & TRADEMARK OFFICE ON 12-16-2022.**

# STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application no. 17/188,922 filed March 1, 2021, which is a continuation of U.S. application no. 16/746,028 filed January 17, 2020, which is a continuation of U.S. application no. 16/665,702 filed October 28, 2019, which is a continuation of 16/248,460 filed January 15, 2019, which are hereby incorporated by reference.

## TECHNICAL FIELD

The subject matter described herein relates generally to compositions for parenteral administration comprising L-cysteine that are stable and have desirable safety attributes for extended periods of time.

## BACKGROUND

L-cysteine is a sulfur-containing amino acid that can be synthesized de novo from methionine and serine in adult humans. L-cysteine performs a variety of metabolic functions. For example, L-cysteine is involved in growth and protein synthesis and it is a precursor for glutathione, an important intracellular antioxidant.

L-cysteine is generally classified as a non-essential amino acid or "semi-essential" amino acid because it can be synthesized in small amounts by the human body. However, some adults can still benefit from L-cysteine supplementation. Further, L-cysteine has been classified as conditionally essential in some cases. For example, L-cysteine can be conditionally essential in preterm infants due to biochemical immaturity of the enzyme cystathionase that is involved in L-cysteine synthesis. Thus, there are a number of circumstances in which L-cysteine supplementation can be desirable.

The subject matter described herein addresses the shortcomings of the art by providing L-cysteine compositions that facilitate the desired supplementation but with an exceptional safety, purity and stability profile.

## BRIEF SUMMARY

In certain aspects, the subject matter described herein is directed to a safe, stable L-cysteine composition for parenteral administration, comprising:

L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof in an amount from about 10 mg/mL to about 100 mg/mL;

Aluminum (Al) in an amount from about 1.0 part per billion (ppb) to about 250 ppb;

L-cystine in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine;

pyruvic acid in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine;

a pharmaceutically acceptable carrier, comprising water;

headspace $O_2$ that is from about 0.5% to 4.0% from the time of manufacture to about 1 month from manufacture when stored at room temperature;

dissolved oxygen present in the carrier in an amount from about 0.1 parts per million (ppm) to about 5 ppm from the time of manufacture to about 1 month from manufacture when stored at room temperature,

wherein the composition is enclosed in a single-use container having a volume of from about 10 mL to about 100 mL.

In certain aspects, the subject matter described herein is directed to a safe, stable L-cysteine composition for parenteral administration, comprising:

L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof in an amount from about 10 mg/mL to about 100 mg/mL;

Aluminum (Al) in an amount from about 1.0 parts per billion (ppb) to about 250 ppb;

L-cystine in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine;

pyruvic acid in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine;

a pharmaceutically acceptable carrier, comprising water;

headspace $O_2$ that is from about 0.5% to 4.0% from the time of manufacture to about 1 month from manufacture when stored at room temperature;

dissolved oxygen present in the carrier in an amount from about 0.1 parts per million (ppm) to about 5 ppm from the time of manufacture to about 1 month from manufacture when stored at room temperature,

optionally one or more metals selected from the group consisting of Lead from about 1.0 ppb to about 10 ppb, Nickel from about 5 ppb to about 40 ppb, Arsenic from about 0.1 ppb to 10 ppb, and Mercury from about 0.2 ppb to about 5.0 ppb;

wherein the composition is enclosed in a single-use container having a volume of from about 10 mL to about 100 mL.

In certain aspects, the subject matter described herein is directed to a safe, stable composition from about 100 mL to about 1000 mL for administration via a parenteral infusion within about 24 to about 48 hours of admixture, comprising a mixture of a composition of L-Cysteine described herein; and an amino acid composition that is essentially free of L-Cysteine comprising one or more amino acids selected from the group consisting of: leucine, isoleucine, lysine, valine, phenylalanine, histidine, threonine, methionine, tryptophan, alanine, arginine, glycine, proline, serine, and tyrosine.

In certain aspects, the subject matter described herein is directed to a method of reducing Aluminum administration from a total parenteral nutrition regimen comprising L-cysteine, the method comprising, mixing a composition comprising L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof comprising:

Aluminum in an amount from about 1.0 parts per billion (ppb) to about 250 ppb;

L-cystine in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine; and

pyruvic acid in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine;

with a composition comprising one or more amino acids selected from the group consisting of: leucine, isoleucine, lysine, valine, phenylalanine, histidine, threonine, methionine, tryptophan, alanine, arginine, glycine, proline, serine, and tyrosine; and

a pharmaceutically acceptable carrier, comprising water,

to form a composition for infusion having a volume of about 100 mL to about 1000 mL, wherein the Aluminum provided in said parenteral nutrition regimen is from about 1-2 to about 4-5 micrograms/kg/day.

In certain aspects, the subject matter described herein is directed to methods of treating a subject having an adverse health condition that is responsive to L-cysteine administration, comprising:

diluting a stable L-cysteine composition as described herein with an intravenous fluid to prepare a diluted L-cysteine composition for infusion; and

infusing the diluted L-cysteine composition for infusion to a subject to provide a therapeutically effective dose of L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof to the subject in a therapeutically effective dosing regimen.

In certain aspects, the subject matter described herein are directed to methods of administering L-Cysteine together with a composition for parenteral nutrition, comprising:

diluting a stable L-cysteine composition for injection as described herein with a parenteral nutrition composition to form a mixture; and

parenterally administering the mixture to a subject in need thereof in a therapeutically and/or nutritionally effective dose. In one aspect, the subject is a preterm infant or newborn to about 1 month of age. Some of these subjects may weigh from about 0.5 kilos to about 2.0 kilos. In another aspect, the subject is a pediatric patient that is of about 1 month to six months of age. Some of these subjects may weigh from about 0.2 kilos to about 20 kilos. In another aspect, the subject is an adult requiring parenteral nutrition.

These and other aspects are more fully described herein.

## BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts the overall trend of the results from the experiments that demonstrate the effectiveness of the Head Space Reduction (HSR) cycle in attaining reduced and consistent dissolved oxygen (DO) levels in the finished drug product. The results showed a trend with an increase in dissolved oxygen level from 0.36 parts per million (ppm) recorded during compounding, to an average of 5.12 ppm measured after filling, a further increase to an average of 9.92 ppm while loading the Lyophilizer, and finally a reduction of dissolved oxygen to an average of 0.50 ppm after headspace reduction. This demonstrates the specific phase of manufacturing at which and to the specific level that oxygen needs to be controlled in the product.

Figure 2 depicts the overall trend of the results from the experiments that demonstrate the effectiveness of the Head Space Reduction (HSR) cycle in attaining reduced and consistent dissolved oxygen (DO) levels in the finished drug product. The results showed a trend with an increase in dissolved oxygen level from 0.36 parts per million (ppm) recorded during compounding, to an average of 5.12 ppm measured after filling, a further increase to an average of 9.92 ppm while loading the Lyophilizer, and finally a reduction of dissolved oxygen to an average of 0.50 ppm after headspace reduction.

Figure 3 depicts a process filler set up to fill and reduce head space oxygen.

Figure 4 shows data for the process of Example 4. The plot shows comparison of oxygen headspace control between the lyophilizer chamber headspace control method versus the high-speed filler vacuum stoppering system. The time zero oxygen headspace results for the batch PROT-000213 are shown in comparison to the previously manufactured lots. Results shown were measured at the time of manufacturing on samples of vials from the batches.

Figure 5 depicts the data measured for dissolved oxygen levels in the process of Example 4.

## DETAILED DESCRIPTION

The presently disclosed subject matter will now be described more fully hereinafter. However, many modifications and other embodiments of the presently disclosed subject matter set forth herein will come to mind to one skilled in the art to which the presently disclosed subject matter pertains having the benefit of the teachings presented in the foregoing descriptions. Therefore, it is to be understood that the presently disclosed subject matter is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims. In other words, the subject matter described herein covers all alternatives, modifications, and equivalents that are within the ordinary skill in the art. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls. Unless otherwise defined, all technical and scientific terms used herein are intended to have the same meaning as commonly understood by one of ordinary skill in this field. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

Advantageously, it has been found that the desirable attributes of L-cysteine compositions for infusion can be obtained without the characteristic impurity profile that is known in the art. Such impurity profile makes the product less safe to be used by patients, in particular, preterm and term infants and pediatric patients of 1 month to 1 year as well as critically ill adults. Specifically, the art formulations fail to address the issues related to the amounts of Aluminum and cystine, among other impurities, that can be routinely present and co-administered with L-cysteine. It has now been found that L-cysteine compositions for injection can be prepared using the methods described herein whereby the compositions unexpectedly comprise exceedingly low levels of Aluminum and other undesirable impurities, such as cystine, pyruvic acid, certain heavy metals and certain ions. As a result, the present compositions and methods of using said compositions are safer to the intended subject compared to the currently available compositions and

methods. Further, the product is also rendered more stable by virtue of lower levels of cystine generated by the manufacturing processes described herein.

As described herein, without being bound to theory, it has been found that the problems of safety, purity and stability are results not simply or directly from the level of Aluminum, but are also intertwined with dissolved oxygen levels in the composition and oxygen in the headspace as well as certain heavy metals and certain ions that may leach or be extracted out of the container closure.

An L-Cysteine for injection product was prepared with the aim to provide a product that would be acceptable for administration to infants, pediatric and adult patients. High quality Schott glass vials and stoppers were used. See Example 2. It was however found that glass containers contribute more significantly than expected to the Aluminum content of L-cysteine compositions stored therein to the point where the product did not meet the specifications for certain components. Products having such Aluminum levels would likely be deemed unsafe by the FDA. As such, efforts were focused on identifying the sources of Aluminum in the product and attempts to minimize it in the product. These efforts led to the unexpected discovery that simply removing a source of Aluminum by replacing glass with plastic did not result in a product having the desired properties.

Additional efforts to identify the root cause for the product failure led to the finding that the product likely failed because oxygen entered the plastic container and into the product at a rate higher than previously expected or predicted. For example, the plastic container product failed in some cases in less than 1-2 months. See Example 3. This finding was also unexpected. Increased oxygen levels in the product led to unacceptable levels of oxidation products, such as cystine, which precipitated and caused particulates in the product. Particulates are dangerous in injectable compositions and create a safety concern, in addition to the stability issue to the product.

However, the precipitation may have been exacerbated by reduction in Aluminum since Aluminum in solution may have a stabilizing effect. Consequently, removing Aluminum may have the unintended consequence of increased precipitation and product

failure in the presence of even small amounts of oxygen in the container. This was unexpected.

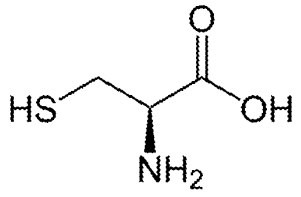
Additionally, controlling heat in the process including during the compounding and/or sterilization activities, unexpectedly was found to be beneficial for preparing stable L-Cysteine compositions described herein. This was surprising because L-Cysteine has been used in parenteral products as an excipient where the product is subjected to terminal sterilization which exposes the product to high temperatures such as 120 °C.

Some subjects that would be receiving L-Cysteine supplementation are, as discussed elsewhere herein, pre-term neonates or full-term infants that are underweight, or infants that may be full term and are not underweight but are still candidates for treatment, in many cases for longer term treatment. For example, some of these subjects may be treated with L-Cysteine for several days or several weeks, even several months. In these cases, it is imperative that the subjects are not exposed to potentially toxic or undesirable levels of some anions and heavy metals that may be present in drug products. Examples of such heavy metals include but not limited to Lead, Nickel, Arsenic and Mercury. Examples of anions that should be monitored include but not limited to iodide, and fluoride. Many of these are introduced into drug products through manufacturing processes, container closure systems, or the drug substance and the excipients. The levels of the heavy metals and anions may not be a concern with many drug products because the patient population exposed to the drug may be not as vulnerable as in the case of L-Cysteine, or the dosing of such drug products may be very limited, i.e., for one or a few doses. For the reasons noted above, it is imperative that L-Cysteine drug product, its administration, its manufacture, and its container closure system are carefully evaluated for the levels of heavy metals and selected anions. The state of the art is lacking in providing any specific guidance on the need for this evaluation, the specific heavy metals and anions on which to focus, and how to achieve control over the levels. The L-Cysteine compositions, methods of administration and manufacture, selection of container closure system and the excipients and the drug substance as described herein fill that need.

Thus, in summary, as described herein, reducing aluminum drastically to extremely low levels in the product, reducing oxygen to very low levels in the process and in the composition, and/or reducing or eliminating heat in the process, and in consideration of data showing selection of the appropriate container, stopper, drug substance, and excipients, individually or in combination(s), resulted in achieving a safe, stable composition of L-Cysteine injection that could be administered safely even to very delicate pediatric subjects such as pre-term neonatal subjects that are as young as a day and may weigh as low as 0.5 kilos, for a few days to several weeks.

L-cysteine for injection is a marketed product used as a component of a nutritional supplement regimen referred to as total parenteral nutrition (TPN). The Aluminum content in known L-cysteine compositions for injection is higher than desired. Moreover, when the L-cysteine composition is combined with certain amino acids prior to administration, the amino acids contribute some amount of Aluminum, and Aluminum levels can further increase. TPN admixtures constitute several other components (in addition to amino acid mixtures) such as electrolytes (such as Potassium Phosphate, Calcium gluconate, and sodium acetate). These electrolytes may also contribute to high Aluminum levels in TPN admixtures (Smith et al., Am. J. Health Syst. Pharm., vol. 64, April, 1, 2007, pp. 730-739). This is of particular concern since administration of the L-cysteine is often to infants (some of them pre-term) for nutritional support. A focus of the subject matter described herein is in minimizing the Aluminum levels coming from L-Cysteine compositions so that when admixed with other ingredients of TPN admixtures, the overall Aluminum levels could be reduced while minimizing introduction of undesirable materials such as heavy metals, anions, and particulates. All of these components are present in amounts that are below levels determined to be safe.

L-cysteine (2-Amino-3-sulfhydrylpropanoic acid) is a sulfur-containing amino acid having a structure according to Formula I:




(I)

L-cysteine performs a variety of metabolic functions. For example, L-cysteine is a precursor for antioxidants, such as glutathione and taurine, that support oxidative defense and a healthy immune system. L-cysteine can also play a role in the synthesis of essential fatty acids and facilitate production of cell membranes and protective covers of nerve endings. Additionally, L-cysteine can be an important precursor for many proteins, such as structural proteins in connective tissue. Thus, the depletion or absence of cystathionase activity in premature fetuses and newborns to synthesize L-cysteine de novo has led to the categorization of L-cysteine as a conditionally essential amino acid. Additionally, administration of L-cysteine can be valuable to treat a number of conditions in subjects, whether or not the subject is a premature infant or neonate.

Known pharmaceutical compositions that contain L-cysteine can typically contain undesirable levels of certain components. Cystine is an oxidation product of L-cysteine. Like L-cysteine, cystine can be synthesized in the liver. Further, both L-cysteine and cystine can be present as amino acid residues in proteins. However, because cystine is an oxidation product of L-cysteine, it is possible that the amount of cystine can increase over time. Thus, it may be desirable to maintain the amount of cystine within predetermined levels over time. For all practical purposes, cystine and L-Cystine are used interchangeably herein. Pyruvic acid is another undesirable compound that can be found in L-cysteine compositions known in the art. It is possible that the amount of pyruvic acid in these compositions can increase over time. Thus, it may be desirable to maintain the amount of pyruvic acid within predetermined levels over time.

Perhaps of most concern is the level of Aluminum in known L-cysteine compositions. Aluminum contamination and associated Aluminum toxicity can lead to a number of adverse conditions such as metabolic bone disease, neurodevelopmental delay,

cholestasis, osteoporosis, growth failure, dementia, and the like. It is desirable to allow no more than 4-5 mcg/kg/day of Aluminum to avoid toxicity. It is preferable to keep the dose on the conservative side as much as possible, i.e., at 4 mcg/kg/day to avoid accidental overdosing in case Aluminum from some other reason (unanticipated or unknown source or due to human error) is introduced. Up to now, known L-cysteine compositions contain up to 5000 ppb Aluminum. Even levels of 900 ppb are known in currently available products. In stark contrast, described herein are compositions that provide a therapeutically effective amount of L-cysteine, while containing less than 250 ppb Aluminum, including, in certain embodiments, less than 200 ppb, or less than 175 ppb, or less than 150 ppb, or less than 125 ppb, or less than 120 ppb, or less than 100 ppb, or less than 80 ppb, or less than 75 ppb, or less than 60 ppb, or less than 50 ppb, or less than 40 ppb, or less than 30 ppb, or less than 20 ppb, or less than10 ppb, or less than 5 ppb, or less than 1.0 ppb. Thus, what has now been achieved is an unexpected and substantial reduction in Aluminum content of an L-Cysteine composition that permits exposure to less than or equal to 4-5 micrograms per kilogram per day (µg/kg/d) to avoid or minimize Aluminum toxicity while still providing therapeutically effective L-cysteine in a stable composition. In some aspects, the compositions described herein permit an Aluminum dose of as low as 0.6 micrograms/kg/d, improving significantly the safety of the L-Cysteine product and its administration.

High risk patient populations for Aluminum toxicity in the context of parenteral nutrition include the following: Renal Insufficiency and Infants: Renal elimination is a major source of Aluminum removal. Therefore, patients with renal compromise and infants with immature renal function are at risk of Aluminum accumulation. Pregnant women: The fetus is vulnerable to Aluminum contamination in parenteral nutrition since Aluminum may be transferred across the placenta. Elderly: Age is a well-known risk factor for renal impairment and thus results in a higher risk of Aluminum toxicity. Other studies suggest that Aluminum toxicity may be due to increased absorption of Aluminum due to a weakened GI protective barrier.

The compositions and methods described herein provide the means to support the nutritional needs of patients, including preterm infants or infants with low birth weight, but reduce the risks associated with Aluminum ingestion. Most preterm and low birth weight infants tend to require parenteral nutrition with amino acid supplementation during their hospital stay. However, as mentioned above, infants are a particularly high-risk population for Aluminum toxicity. To address such issues, in certain embodiments, the compositions comprise about 34.5 mg/mL of L-cysteine (measured as a base, i.e., not measured as HCl and monohydrate) and no more than 250 ppb, preferably about 120 ppb, or lower, of Aluminum. These compositions with no more than 120 ppb of Aluminum, and in certain embodiments, about 120 ppb, or 100 ppb, or 80 ppb, or 60 ppb, or 50 ppb, or 20 ppb, or 10 ppb or 5 ppb or 1.0 ppb, or any suitable subrange encompassing the specific values, in units of 5 ppb, permit great flexibility with respect to the amino acid supplementation for TPN preparations.

L-Cysteine injection is administered after being added to a parenteral nutrition composition such as an amino acid composition, or a sugar-source such as dextrose or a lipid source or a combination of the foregoing. It is preferred that L-Cysteine is added to the amino acid composition, which may be administered separately or in combination with other components of a parenteral nutrition regime such as sugars and lipids. For present purposes, the Aluminum content of the combined L-Cysteine and amino acid solution is of interest, and is monitored. L-Cysteine may be dosed at 15 mg per gram of amino acids or sometimes at a high concentration, i.e., 40 mg/gram of amino acids.

Commercially available amino acid product labeling for example indicates that 25 mcg/L of Aluminum is contributed from the product itself. The general recommended maximum dose is 4 g of amino acids/kg body weight. Generally amino acids solutions are available as 10% (10 g/100 mL) which would necessitate 40 mL volume to be administered for a 1 kg preterm neonatal patient. Based on this the amino acids solution is expected to contribute to about 1 mcg/kg/day. This leaves about 3 mcg/kg/day from other sources including L-cysteine. In some scenarios, there may be five or more other components including L-cysteine that can contribute to varying levels of Aluminum in TPN mixtures.

For the sake of illustration, assume there are five contributors that contribute equally. The expected maximum Aluminum contribution that may come from L-Cysteine would be (3 mcg/kg/day)/5 = 0.6 mcg/kg/day. In light of Smith et al. (Am. J. Health Syst. Pharm., vol. 64, April, 1, 2007, pp. 730-739), significant contributors to Aluminum levels besides amino acids and L-Cysteine are Potassium Phosphate, Potassium Acetate, Sodium Acetate, and Calcium Gluconate. The reference indicates that contributions from all of these are high such that 100% of pediatric (including preterm and full-term infants) TPNs have >4 µg/kg/day (range 12 – 162 µg/kg/day) of Aluminum coming from various sources. Even after carefully selecting the products with the least Aluminum content components among those available for treatment, the TPNs have > 4 µg/kg/day. This finding for example highlights the need to systematically reduce the amount of Aluminum in each product that will be incorporated into a TPN admixture. The current efforts are directed to providing L-Cysteine compositions that offer exceedingly low Aluminum levels.

One of the difficulties with establishing dosing levels of L-Cysteine with an eye to keep the Aluminum administration to below or at a certain amount is the lack of uniformity in the art as to how to categorize the subjects in terms of their age and weight. This imprecise terminology has been used often blurring the boundaries among the patient groups, making it difficult to assess which patient should receive what amount of L-Cysteine, and hence how much Aluminum would result. As such, the art does not suggest what the levels of Aluminum exposure should be, nor does it provide a solution that minimizes Aluminum exposure during a TPN regimen. Following Table 1 shows a streamlined approach to categorize the potential patient population and their proposed daily doses of L-Cysteine.

Table 1. Daily Dosage of L-Cysteine

| Age | Protein[a] Requirement (g/kg/day)[1] | L-Cysteine Dosage (mg cysteine/g AA) | L-Cysteine Dosage (mg cysteine/kg/day) |
|---|---|---|---|
| Preterm and term infants less than 1 month of age | 3 to 4 | 15 | 45 to 60 |

Table 1. Daily Dosage of L-Cysteine

| | | | |
|---|---|---|---|
| Pediatric patients 1 month to less than 1 year of age | 2 to 3 | 15 | 30 to 45 |
| Pediatric patients 1 year to 11 years of age | 1 to 2 | 15 | 15 to 30 |
| Pediatric patients 12 years to 17 years of age | 0.8 to 1.5 | 5 | 4 to 7.5 |
| Adults: Stable Patients | 0.8 to 1 | 5 | 4 to 5 |
| Adults: Critically Ill Patients | 1.5 to 2 | 5 | 7.5 to 10 |

[a] Protein is provided as amino acids. When infused intravenously, amino acids are metabolized and utilized as the building blocks of protein.

From the above Table, it should be noted that the most need for L-Cysteine is for the preterm infant. Therefore, to safely administer L-Cysteine compositions, the Aluminum level in the compositions must be substantially less than what is in commercially available products and those described in the art. There has been no specific guidance in the art however of how low this Aluminum level should be, and how to achieve compositions with such low Aluminum levels. To the extent there may be some guidance, the levels proposed are considered higher than desirable.

L-Cysteine Injection as presented herein in some embodiments contains no more than 120 mcg/L (120 ppb) of aluminum (0.0035 mcg of aluminum/mg of cysteine). The maximum dosage of aluminum from L-Cysteine Injection is not more than 0.21 mcg/kg/day when preterm and term infants less than 1 month of age are administered the dosage of L-Cysteine injection (15 mg cysteine/g of amino acids and 4 g of amino acids/kg/day). If L-Cysteine is added to TPN containing amino acid and dextrose solutions (which each may contain up to 25 mcg/L of aluminum) as well as other additive drug products, the total amount of aluminum administered to the patient from the final admixture should be considered and maintained at no more than 5 mcg/kg/day.

However, with prolonged parenteral administration in patients with renal impairment, the aluminum contained in L-Cysteine Injections disclosed herein may reach toxic levels. Preterm infants are at a greater risk for aluminum toxicity because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which also contain aluminum. Prolonged administration herein may mean at least one

week, or may be up to 2-4 weeks. In some aspects, the administration could continue for up to 24 weeks.

Patients with renal impairment, including preterm infants, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day, accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration. Therefore, it is essential that aluminum levels in the L-Cysteine drug product are carefully controlled and kept at as low as possible. Such embodiments are disclosed herein.

Looking more specifically at contribution of Aluminum by the prior products, data show that the Aluminum levels of 5,000 ppb or even the 900 ppb associated with these products are not desirable or acceptable. Tables 2-3 report the Aluminum contribution from the commercial product of prior art with 900 ppb or 5000 ppb Aluminum level based on two scenarios: a) an L-Cysteine dosing regimen based on 15 mg/gram of amino acids; and b) an L-Cysteine dosing regimen based on 40 mg/gram of amino acids. The Tables also show the Aluminum contribution from an L-Cysteine product as described herein and having a level of 120 ppb.

Table 2. Aluminum Contribution (Based on a Cysteine Dose of 15 mg/g of Amino Acids) from an L-Cysteine Product with 900 ppb, 5,000 ppb, or 120 ppb of Aluminum

| Age | L-Cysteine Dose at (15 mg/ g AA) | | Aluminum Contribution from 900 ppb product | Aluminum Contribution from 5,000 ppb product | Aluminum Contribution from 120 ppb product |
|---|---|---|---|---|---|
| | mg/kg/day | mL/kg/day | mcg/kg/day | mcg/kg/day | mcg/kg/day |
| Preterm and term infants less than 1 month | 45 to 60 | 1.31 to 1.74 | 1.18 to 1.57 | 6.53 to 8.70 | 0.157 to 0.209 |
| Pediatric patients 1 month to less than 1 yr | 30 to 45 | 0.87 to 1.31 | 0.79 to 1.17 | 4.35 to 6.52 | 0.1 to 0.157 |
| Pediatric patients 1 yr to 11 yrs | 15 to 30 | 0.44 to 0.87 | 0.40 to 0.79 | 2.18 to 4.35 | 0.053 to 0.1 |

| | | | | | |
|---|---|---|---|---|---|
| Pediatric patients 12 yrs to 17 yrs | 4 to 7.5 | 0.18 to 0.22 | 0.11 to 0.20 | 0.58 to 1.09 | 0.022 to 0.026 |
| Adults: Stable Patients | 4 to 5 | 0.18 to 0.23 | 0.11 to 0.14 | 0.58 to 0.73 | 0.022 to 0.028 |
| Adults: Critically ill patients | 7 to 10 | 0.32 to 0.46 | 0.2 to 0.28 | 1.02 to 1.46 | 0.038 to 0.055 |

Table 3. Aluminum Contribution (Based on a Cysteine Dose of 40 mg/g of Amino Acids) from an L-Cysteine Product with 900 ppb, 5,000 ppb, or 120 ppb of Aluminum

| Age | L-Cysteine Dose at (40 mg/ g AA) | | Aluminum Contribution from 900 ppb product | Aluminum Contribution from 5,000 ppb product | Aluminum Contribution from 120 ppb product |
|---|---|---|---|---|---|
| | mg/kg/day | mL/kg/day | mcg/kg/day | mcg/kg/day | mcg/kg/day |
| Preterm and term infants less than 1 month | 120 to 160 | 3.48 to 4.64 | 3.13 to 4.17 | 17.39 to 23.19 | 0.42 to 0.56 |
| Pediatric patients 1 month to less than 1 yr | 80 to 120 | 2.32 to 3.48 | 2.09 to 3.13 | 11.59 to 17.39 | 0.28 to 0.42 |
| Pediatric patients 1 yr to 11 yrs | 40 to 80 | 1.16 to 2.32 | 1.05 to 2.09 | 5.79 to 11.59 | 0.14 to 0.28 |
| Pediatric patients 12 yrs to 17 yrs | 10.66 to 20 | 0.31 to 0.58 | 0.28 to 0.53 | 1.56 to 2.94 | 0.04 to 0.07 |
| Adults: Stable Patients | 10.66 to 13.33 | 0.31 to 0.39 | 0.28 to 0.35 | 1.56 to 1.94 | 0.04 to 0.047 |
| Adults: Critically ill patients | 18.7 to 26.7 | 0.54 to 0.77 | 0.49 to 0.70 | 2.72 to 3.89 | 0.065 to 0.09 |

If the preterm infants are given the high dose of L-cysteine (40 mg / gram of amino acids), this requires that a dose of 160 mg/kg (4.64 mL/kg) of L-Cysteine at a (base) concentration of 34.5 mg/mL be delivered. (See Table 3 above). The compositions described herein contribute about 0.0035 mcg Aluminum per each mg of L-cysteine, or 0.12 mcg of Aluminum per each mL at 120 ppb. Thus, a dose of 160 mg/kg (4.64 mL/kg) L-cysteine delivers only 0.56 mcg/kg Aluminum at 40 mg/g of AA dosing on the higher end, or 0.157 mcg/kg at 15 mg/g of AA dosing on the lower end. See Tables 2-3. In contrast, if art products were to be used, these patients would receive either 23 mcg/kg (for

the product that contains 5,000 ppb of Aluminum), or 4.2 mcg/kg of aluminum (for the product that contains 900 ppb of Aluminum). Given that the total daily intake permissible for Aluminum is expected to be ideally less than 4-5 mcg/kg, the art products already exceed the entire daily Aluminum level and do not leave room for Aluminum contribution from other TPN components. Therefore, these known high Aluminum-containing products are likely to be deemed unsafe by the FDA and are neither desirable nor acceptable. In contrast, the L-Cysteine compositions presented herein provide Aluminum levels ranging from 10 ppb to about 250 ppb. Taking 20 ppb, 50 ppb, 120 ppb, and 150 ppb as illustrations, the Tables below estimate the amount of Aluminum delivered for each class of patients using 34.5 mg/mL L-Cysteine product when being dosed at 15 mg/g of Amino Acids.

Table 4. Aluminum Contribution (Based on a Cysteine Dose of 15 mg/g of Amino Acids) from an L-Cysteine Product (34.5 mg/mL) with 20 ppb, 50 ppb, 120 ppb or 150 ppb of Aluminum

| Age | L-Cysteine Dose at 15mg/g AA | Aluminum Contribution from 20 ppb product | Aluminum Contribution from 50 ppb product | Aluminum Contribution from 120 ppb product | Aluminum Contribution from 150 ppb |
|---|---|---|---|---|---|
| | mg/kg/day | mcg/kg/day | mcg/kg/day | mcg/kg/day | mcg/kg/day |
| Preterm and term infants less than 1 month | 45 to 60 | 0.026 to 0.035 | 0.065 to 0.088 | 0.157 to 0.209 | 0.195 to 0.26 |
| Pediatric patients 1 month to less than 1 yr | 30 to 45 | 0.017 to 0.026 | 0.043 to 0.065 | 0.1 to 0.157 | 0.13 to 0.195 |
| Pediatric patients 1 yr to 11 yrs | 15 to 30 | 0.009 to 0.017 | 0.022 to 0.044 | 0.053 to 0.11 | 0.066 to 0.125 |
| Pediatric patients 12 yrs to 17 yrs | 4 to 7.5 | 0.004 | 0.009 to 0.01 | 0.022 to 0.026 | 0.027 to 0.033 |
| Adults: Stable Patients | 4 to 5 | 0.004 | 0.009 to 0.12 | 0.022 to 0.028 | 0,027 to 0.035 |
| Adults: Critically ill patients | 7 to 10 | 0.006 to 0.009 | 0.016 to 0.23 | 0.038 to 0.055 | 0.048 to 0.069 |

In some embodiments, parenteral L-Cysteine compositions provide about 35 mg/mL of L-Cysteine to deliver 45 to 60 mg/kg/day of L-Cysteine and from about 0.02 to about 0.3 mcg/kg/day of Aluminum. In some embodiments, parenteral L-Cysteine compositions provide about 35 mg/mL of L-Cysteine to deliver 30 to 45 mg/kg/day of L-Cysteine and from about 0.01 to about 0.25 mcg/kg/day of Aluminum. In some embodiments, parenteral L-Cysteine compositions provide about 35 mg/mL of L-Cysteine to deliver 15 to 30 mg/kg/day of L-Cysteine and from about 0.005 to about 0.15 mcg/kg/day of Aluminum.

In some embodiments, parenteral L-Cysteine compositions provide about 35 mg/mL of L-Cysteine to deliver 4 to 7.5 mg/kg/day of L-Cysteine and from about 0.003 to about 0.04 mcg/kg/day of Aluminum. In some embodiments, parenteral L-Cysteine compositions provide about 35 mg/mL of L-Cysteine to deliver 4 to 5 mg/kg/day of L-Cysteine and from about 0.003 to about 0.04 mcg/kg/day of Aluminum. In some embodiments, parenteral L-Cysteine compositions provide about 35 mg/mL of L-Cysteine to deliver 7 to 10 mg/kg/day of L-Cysteine and from about 0.004 to about 0.08 mcg/kg/day of Aluminum.

In some embodiments, a method of safe administration of L-Cysteine comprises administering to preterm and term infants of less than 1 month of age a parenteral L-Cysteine composition that delivers 45 to 60 mg/kg/day of L-Cysteine and from about 0.02 to about 0.3 mcg/kg/day of Aluminum, admixed with a parenteral nutrition composition. In some embodiments, a method of safe administration of L-Cysteine comprises administering to pediatric patients 1 month to less than 1 year of age a parenteral L-Cysteine composition that delivers 30 to 45 mg/kg/day of L-Cysteine and from about 0.01 to about 0.25 mcg/kg/day of Aluminum, admixed with a parenteral nutrition composition. In some embodiments, a method of safe administration of L-Cysteine comprises administering to pediatric patients 1 year to 11 years of age a parenteral L-Cysteine composition that delivers 15 to 30 mg/kg/day of L-Cysteine and from about 0.005 to about 0.15 mcg/kg/day of Aluminum, admixed with a parenteral nutrition composition.

In some embodiments, a method of safe administration of L-Cysteine comprises administering to pediatric patients 12 years to 17 years of age a parenteral L-Cysteine composition that delivers 4 to 7.5 mg/kg/day of L-Cysteine and from about 0.003 to about 0.04 mcg/kg/day of Aluminum, admixed with a parenteral nutrition composition. In some embodiments, a method of safe administration of L-Cysteine comprises administering to adult stable patients a parenteral L-Cysteine composition that delivers 4 to 5 mg/kg/day of L-Cysteine and from about 0.003 to about 0.04 mcg/kg/day of Aluminum, admixed with a parenteral nutrition composition. In some embodiments, a method of safe administration of L-Cysteine comprises administering to critically ill adult patients a parenteral L-Cysteine composition that delivers 7 to 10 mg/kg/day of L-Cysteine and from about 0.004 to about 0.08 mcg/kg/day of Aluminum, admixed with a parenteral nutrition composition.

Further, taking 20 ppb, 50 ppb, 120 ppb, and 150 ppb as illustrations, the Tables below estimate the amount of Aluminum delivered for each class of patients using 34.5 mg/mL L-Cysteine product when being dosed at 40 mg/g of Amino Acids.

Table 5. Aluminum Contribution (Based on a Cysteine Dose of 40 mg/g of Amino Acids) from an L-Cysteine Product (34.5 mg/mL) with 20 ppb, 50 ppb, 120 ppb or 150 ppb of Aluminum

| Age | L-Cysteine Dose at 40 mg/g AA | Aluminum Contribution from 20 ppb product | Aluminum Contribution from 50 ppb product | Aluminum Contribution from 120 ppb product | Aluminum Contribution from 150 ppb |
|---|---|---|---|---|---|
| | mg/kg/day | mcg/kg/day | mcg/kg/day | mcg/kg/day | mcg/kg/day |
| Preterm and term infants less than 1 month | 120 to 160 | 0.07 to 0.09 | 0.175 to 0.233 | 0.42 to 0.56 | 0.525 to 0.7 |
| Pediatric patients 1 month to less than 1 yr | 80 to 120 | 0.047 to 0.07 | 0.117 to 0.175 | 0.28 to 0.42 | 0.35 to 0.525 |
| Pediatric patients 1 yr to 11 yrs | 40 to 80 | 0.023 to 0.047 | 0.058 to 0.117 | 0.14 to 0.28 | 0.175 to 0.35 |
| Pediatric patients 12 | 10.66 to 20 | 0.007 to 0.012 | 0.017 to 0.029 | 0.04 to 0.07 | 0.05 to 0.088 |

| | | | | | |
|---|---|---|---|---|---|
| yrs to 17 yrs | | | | | |
| Adults: Stable Patients | 10.66 to 13.33 | 0.007 to 0.008 | 0.017 to 0.02 | 0.04 to 0.047 | 0.05 to 0.059 |
| Adults: Critically ill patients | 18.7 to 26.7 | 0.011 to 0.015 | 0.027 to 0.038 | 0.065 to 0.09 | 0.081 to 0.113 |

In some embodiments, parenteral L-Cysteine compositions provide about 35 mg/mL of L-Cysteine to deliver 120 to 160 mg/kg/day of L-Cysteine and from about 0.05 to about 0.8 mcg/kg/day of Aluminum. In some embodiments, parenteral L-Cysteine compositions provide about 35 mg/mL of L-Cysteine to deliver 80 to 120 mg/kg/day of L-Cysteine and from about 0.03 to about 0.6 mcg/kg/day of Aluminum. In some embodiments, parenteral L-Cysteine compositions provide about 35 mg/mL of L-Cysteine to deliver 40 to 80 mg/kg/day of L-Cysteine and from about 0.01 to about 0.4 mcg/kg/day of Aluminum.

In some embodiments, parenteral L-Cysteine compositions provide about 35 mg/mL of L-Cysteine to deliver 10 to 20 mg/kg/day of L-Cysteine and from about 0.005 to about 0.1 mcg/kg/day of Aluminum. In some embodiments, parenteral L-Cysteine compositions provide about 35 mg/mL of L-Cysteine to deliver 10 to 15 mg/kg/day of L-Cysteine and from about 0.005 to about 0.06 mcg/kg/day of Aluminum. In some embodiments, parenteral L-Cysteine compositions provide about 35 mg/mL of L-Cysteine to deliver about 18 to 28 mg/kg/day of L-Cysteine and from about 0.01 to about 0.15 mcg/kg/day of Aluminum.

In some embodiments, a method of safe administration of L-Cysteine comprises administering to preterm and term infants of less than 1 month of age a parenteral L-Cysteine composition that delivers 120 to 160 mg/kg/day of L-Cysteine and from about 0.05 to about 0.8 mcg/kg/day of Aluminum, admixed with a parenteral nutrition composition. In some embodiments, a method of safe administration of L-Cysteine comprises administering to pediatric patients 1 month to less than 1 year of age a parenteral L-Cysteine composition that delivers 80 to 120 mg/kg/day of L-Cysteine and from about

0.03 to about 0.6 mcg/kg/day of Aluminum, admixed with a parenteral nutrition composition. In some embodiments, a method of safe administration of L-Cysteine comprises administering to pediatric patients 1 year to 11 years of age a parenteral L-Cysteine composition that delivers 40 to 80 mg/kg/day of L-Cysteine and from about 0.01 to about 0.4 mcg/kg/day of Aluminum, admixed with a parenteral nutrition composition.

In some embodiments, a method of safe administration of L-Cysteine comprises administering to pediatric patients 12 years to 17 years of age a parenteral L-Cysteine composition that delivers 10 to 20 mg/kg/day of L-Cysteine and from about 0.005 to about 0.1 mcg/kg/day of Aluminum, admixed with a parenteral nutrition composition. In some embodiments, a method of safe administration of L-Cysteine comprises administering to adult stable patients a parenteral L-Cysteine composition that delivers 10 to 15 mg/kg/day of L-Cysteine and from about 0.005 to about 0.06 mcg/kg/day of Aluminum, admixed with a parenteral nutrition composition. In some embodiments, a method of safe administration of L-Cysteine comprises administering to critically ill adult patients a parenteral L-Cysteine composition that delivers 18 to 28 mg/kg/day of L-Cysteine and from about 0.01 to about 0.15 mcg/kg/day of Aluminum, admixed with a parenteral nutrition composition.

Accordingly, what is provided herein, among other things, are therapeutically and/or nutritionally effective amounts of L-cysteine with significantly minimized risk of Aluminum toxicity.

I. Definitions

As used herein, the term “stable” refers to a composition that has the component profiles described herein, for example, Aluminum, L-Cystine, and pyruvic acid, at the levels described and for the amount of time identified. In other words, a stable composition will contain the specified levels of all components for sufficient period of time to enable the composition to be commercially manufactured, stored, shipped, and administered in a clinical setting. In general, products are considered stable if the period of time is three months, or three to six months, or three to 12 months, or three to 15 months, or three to 18 months or three to 24 months.

As used herein, the term "dissolved oxygen" refers to oxygen that is found in the aqueous carrier of the compositions. Distinguished from dissolved oxygen is the headspace oxygen. As used herein, the term "headspace oxygen" refers to the oxygen that is found in the headspace volume of the sealed container comprising the composition.

As used herein, the term "cystine precipitate" refers to undissolved L-cystine. The undissolved cystine may be visually detected as particulate matter in solution.

As used herein, "subject" refers to a mammal that may benefit from the administration of a composition described herein. In one aspect, the mammal may be a human.

The term "prophylaxis" or "prophylactic" refers to the continued absence of symptoms of the disease or condition that would be expected had the combination not been administered.

As used herein, the terms "formulation" and "composition" are used interchangeably and refer to a mixture of two or more compounds, elements, or molecules. In some aspects, the terms "formulation" and "composition" may be used to refer to a mixture of one or more active agents with a carrier or other excipients. Compositions can take nearly any physical state, including solid and/or liquid (i.e. solution). Furthermore, the term "dosage form" can include one or more formulation(s) or composition(s) provided in a form suitable for administration to a subject. As used herein, the term "compositions for injection" and the like, refers to a composition that is intended for injection, including dilution and admixing with other components prior to injection. Said injection may be administered as an intravenous injection, or as an intravenous infusion. When administered as infusions, the compositions may be administered through a peripheral vein in limited circumstances or more commonly through a central vein. One of skill in the art would have experience with such administrations.

As used herein, "effective amount" refers to an amount of an ingredient, such as L-cysteine, which, when included in a composition, is sufficient to achieve an intended compositional or physiological effect. Thus, a "therapeutically or nutritionally effective

amount" refers to a non-toxic, but sufficient amount of an active agent, to achieve therapeutic or nutritional results in treating or preventing a condition for which the active agent is known to be effective or providing nutritional value to prevent effects of malnutrition. It is understood that various biological factors may affect the ability of a substance to perform its intended task. Therefore, an "effective amount" or a "therapeutically or nutritionally effective amount" may be dependent in some instances on such biological factors. Additionally, in some cases an "effective amount" or a "therapeutically or nutritionally effective amount" may not be achieved in a single dose. Rather, in some examples, an "effective amount" or a "therapeutically or nutritionally effective amount" can be achieved after administering a plurality of doses over a period of time, such as in a pre-designated dosing regimen. Further, while the achievement of therapeutic/nutritional effects may be measured by a physician or other qualified medical personnel using evaluations known in the art, it is recognized that individual variation and response to treatments may make the achievement of therapeutic or nutritional effects a subjective decision. The determination of an effective amount is well within the ordinary skill in the art of pharmaceutical and nutritional sciences as well as medicine.

As used herein, the term "substantially" refers to the complete or nearly complete extent or degree of a component, or an action, characteristic, property, state, structure, item, or result. The exact allowable degree of deviation from absolute presence of such a component, or an action, characteristic, property, state, structure, item, or result may in some cases depend on the specific context. However, generally speaking, "substantially" will be so near as to have the same overall result as if absolute and total extent or degree were obtained. The use of "substantially" is equally applicable when used in a negative connotation to refer to the complete or near complete lack of a component, or an action, characteristic, property, state, structure, item, or result. For example, a composition that is "substantially free of" a component would either completely lack the component, or so nearly completely lack the component that the effect would be the same as if it completely lacked the component. In other words, a composition that is "substantially free of" an ingredient or element may still actually contain such component

as long as there is no measurable effect thereof, for example, trace amounts. As used herein, "essentially free" means a component, or an action, characteristic, property, state, structure, item, or result is not present or is not detectable.

The terms "treat" and "treatment" refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change, disorder or adverse health condition. For purposes of this disclosure, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of the condition, stabilized (*i.e.*, not worsening) state of the condition, delay or slowing of progression of the condition, amelioration or palliation of the condition, and absence of condition (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

The term "pharmaceutically acceptable salts" denotes salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts. The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith. The phrase "pharmaceutically acceptable salt," as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a molecule. A pharmaceutically acceptable salt may involve the inclusion of another molecule that acts as a counterion. The counterion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counterions. In the case of L-cysteine, the hydrochloride salt form is preferred.

The phrase "single-use container" refers to a sealed pharmaceutically prepared container holding a drug product in a sterile environment that is intended to be used in a

single operation of transferring the entire contents or substantially entire contents, wherein the transfer operation spans no more than 10-12 hrs, but often less than 8 hrs, or even six hours. It should be recognized that the single-use container is generally preservative-free and that if multiple transfers are attempted, they should be completed in a short duration, i.e., less than about 8-10 hrs from the first breach of the sterile environment. In some aspects the single-use container may be used to administer all of its contents to one subject in need thereof. In some aspects the single-use container may be used to administer its contents to more than one subject in need thereof.

As used herein, the term "mixing" refers to admixing, contacting, blending, stirring or allowing to admix, mix, blend, stir and the like.

As used herein, the term "safe" refers generally to a property of the compositions and methods described herein relative to art method and compositions and/or to FDA regulatory determination of the compositions and methods as part of a therapeutically or nutritionally effective regimen. For example, with respect to known L-Cysteine compositions, an Aluminum level of greater than 300 ppb would be generally considered to render the L-Cysteine product unsafe. Other examples with respect to safety are described and discussed herein with respect to Aluminum, pyruvate, Cystine, heavy metals, anions, and particulates.

Additional definitions are provided herein where appropriate.

## II. Compositions

In certain aspects, the subject matter described herein is directed to a safe, stable L-cysteine composition for parenteral administration, comprising:

L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof in an amount from about 10 mg/mL to about 100 mg/mL;

Aluminum (Al) in an amount from about 1.0 parts per billion (ppb) to about 250 ppb;

L-cystine in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine;

pyruvic acid in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine;

a pharmaceutically acceptable carrier, comprising water;

headspace $O_2$ that is from about 0.5% to 4.0% from the time of manufacture to about 1 month from manufacture when stored at room temperature;

dissolved oxygen present in the carrier in an amount from about 0.1 parts per million (ppm) to about 5 ppm from the time of manufacture to about 1 month from manufacture when stored at room temperature;

wherein the composition is enclosed in a single-use container having a volume of from about 10 mL to about 100 mL.

In certain aspects, the subject matter described herein is directed to a safe, stable L-cysteine composition for parenteral administration, comprising:

L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof in an amount from about 10 mg/mL to about 100 mg/mL;

Aluminum (Al) in an amount from about 1.0 parts per billion (ppb) to about 250 ppb;

L-cystine in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine;

pyruvic acid in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine;

a pharmaceutically acceptable carrier, comprising water;

headspace $O_2$ that is from about 0.5% to 4.0% from the time of manufacture to about 1 month from manufacture when stored at room temperature;

dissolved oxygen present in the carrier in an amount from about 0.1 parts per million (ppm) to about 5 ppm from the time of manufacture to about 1 month from manufacture when stored at room temperature;

optionally present can be one or more metals selected from the group consisting of Lead from about 1.0 ppb to about 10 ppb, Nickel from about 5 ppb to about 40 ppb, Arsenic from about 0.1 ppb to 10 ppb, and Mercury from about 0.2 ppb to about 5.0 ppb;

wherein the composition is enclosed in a single-use container having a volume of from about 10 mL to about 100 mL.

The Aluminum in a composition can be determined using any known analytical method, such as those required by FDA regulations, and can include atomic absorption and mass spectrometry. In certain embodiments, the Aluminum that is present in the compositions is present in an amount from about 1.0 ppb to about 250 ppb, or from about 1.0 ppb to about 180 ppb, or from about 1.0 ppb to about 170 ppb, or from about 1.0 ppb to about 160 ppb, or from about 1.0 ppb to about 150 ppb, or from about 1.0 ppb to about 130 ppb, or from about 1.0 ppb to about 100 ppb, or from about 1.0 ppb to about 50 ppb, or from about 1.0 ppb to about 20 ppb.

In some embodiments the L-Cysteine and Aluminum are at a ratio of from about 35 million:1 (i.e., about 35 million units of L-Cysteine to 1 unit of Aluminum). In some embodiments the L-Cysteine and Aluminum are at a ratio of about 4 million:1. In some embodiments the L-Cysteine and Aluminum are at a ratio of about 1.8 million:1 (i.e., about 1.8 million units of L-Cysteine to 1 unit of Aluminum). In some embodiments the L-Cysteine and Aluminum are at a ratio of about 700,000:1 (i.e., about 700,000 units of L-Cysteine to 1 unit of Aluminum). In some embodiments the L-Cysteine and Aluminum are at a ratio of about 300,000:1 (i.e., about 300,000 units of L-Cysteine to 1 unit of Aluminum). In some embodiments the L-Cysteine and Aluminum are at a ratio of about 230,000:1 (i.e., about 230,000 units of L-Cysteine to 1 unit of Aluminum). In some embodiments the L-Cysteine and Aluminum are at a ratio of about 170,000:1 (i.e., about 170,000 units of L-Cysteine to 1 unit of Aluminum). In some embodiments the L-Cysteine and Aluminum are at a ratio of about 140,000:1 (i.e., about 140,000 units of L-Cysteine to 1 unit of Aluminum).

Thus, in some embodiments the L-Cysteine and Aluminum are at a ratio of from about 35 million:1 (i.e., about 35 million units of L-Cysteine to 1 unit of Aluminum) to about 1.8 million:1 (i.e., about 1.8 million units of L-Cysteine to 1 unit of Aluminum). In some embodiments the L-Cysteine and Aluminum are at a ratio of from about 4 million:1 (i.e., about 4 million units of L-Cysteine to 1 unit of Aluminum) to about 1.8 million:1 (i.e., about 1.8 million units of L-Cysteine to 1 unit of Aluminum). In some embodiments the L-Cysteine and Aluminum are at a ratio of from about 1.8 million:1 (i.e., about 1.8 million

units of L-Cysteine to 1 unit of Aluminum) to about 700,000:1 (i.e., about 700,000 units of L-Cysteine to 1 unit of Aluminum). In some embodiments the L-Cysteine and Aluminum are at a ratio of from about 700,000:1 (i.e., about 700,000 units of L-Cysteine to 1 unit of Aluminum) to about 300,000:1 (i.e., about 300,000 units of L-Cysteine to 1 unit of Aluminum). In some embodiments the L-Cysteine and Aluminum are at a ratio of from about 300,000:1 (i.e., about 300,000 units of L-Cysteine to 1 unit of Aluminum) to about 230,000:1 (i.e., about 230,000 units of L-Cysteine to 1 unit of Aluminum). In some embodiments the L-Cysteine and Aluminum are at a ratio of from about 230,000:1 (i.e., about 230,000 units of L-Cysteine to 1 unit of Aluminum) to about 170,000:1 (i.e., about 170,000 units of L-Cysteine to 1 unit of Aluminum). Thus, in some embodiments the L-Cysteine and Aluminum are at a ratio of from about 170,000:1 (i.e., about 170,000 units of L-Cysteine to 1 unit of Aluminum) to about 140,000:1 (i.e., about 140,000 units of L-Cysteine to 1 unit of Aluminum). All subranges and individual values with increments of 5,000 units are contemplated by the present disclosure. In some embodiments, the unit of measure is nanograms. For example, in some embodiments the L-Cysteine and Aluminum are at a ratio of from about 4 million:1 nanograms (i.e., about 4 million nanograms of L-Cysteine to 1 nanogram of Aluminum) to about 1.8 million:1 nanograms (i.e., about 1.8 million nanograms of L-Cysteine to 1 nanogram of Aluminum).

In certain embodiments, the compositions comprise Aluminum in trace amounts, for example 1.0 ppb, but not more than 250 ppb after storage at ambient temperature for a period of 12 months or less, where the Aluminum comprises, from about 1.0 ppb to about 100 ppb of Aluminum from the container, from about 1.0 ppb to about 100 ppb of Aluminum from a cap of the container, from about 1.0 ppb to about 100 ppb of Aluminum from the L-cysteine, and from about 1.0 ppb to about 20 ppb of Aluminum from the water.

In certain embodiments, the compositions comprise Aluminum in an amount not more than 200 ppb after storage at ambient temperature for a period of 12 months, wherein the Aluminum comprises, from about 1.0 ppb to about 100 ppb of Aluminum from the container, from about 1.0 ppb to about 100 ppb of Aluminum from a cap of the container, from about 1.0 ppb to about 100 ppb of Aluminum from the L-cysteine, and from about

1.0 ppb to about 20 ppb of Aluminum from the water. In certain embodiments, the compositions comprise Aluminum in an amount not more than 200 ppb after storage at ambient temperature for a period of 6 months, where the Aluminum comprises, from about 1.0 ppb to about 100 ppb of Aluminum from the container, from about 1.0 ppb to about 100 ppb of Aluminum from a cap of the container, from about 1.0 ppb to about 100 ppm of Aluminum from the L-cysteine, and from about 1.0 ppb to about 20 ppb of Aluminum from the water. In certain embodiments, the compositions comprise Aluminum in an amount not more than 200 ppb after storage at ambient temperature for a period of 3 months, wherein the Aluminum comprises, from about 1.0 ppb to about 100 ppb of Aluminum from the container, from about 1.0 ppb to about 100 ppb of Aluminum from a cap of the container, from about 1.0 ppb to about 100 ppm of Aluminum from the L-cysteine, and from about 1.0 ppb to about 20 ppb of Aluminum from the water.

In certain embodiments, the dissolved oxygen is present in an amount from about 0.1 ppm to about 5.0 ppm, or from about 0.10 ppm to about 4.0 ppm, or from about 0.10 ppm to about 3.0 ppm, or from about 0.10 ppm to about 2.0 ppm, or from about 0.11 ppm to about 1.0 ppm. In particular, values of dissolved oxygen from about 0.4 ppm to about 3.8 ppm are preferred. For the sake of clarity and the ease of discussion and measurement, these values are taken for the L-Cysteine composition at the time of its manufacture (commonly known as “time zero” data point), or during and up to 1 month from time zero. Additional time points beyond the 1-month from time zero data point are expected to provide similar dissolved oxygen levels.

To achieve the above objective, as described herein, numerous aspects for possible oxygen introduction into the L-cysteine composition have been carefully studied and controlled. For example, in some cases, the dissolved oxygen content in the carrier can be reduced to at or below a predetermined level before the L-cysteine is added to the carrier. In some additional examples, reducing a level of dissolved oxygen in the carrier can include blanketing a container for housing the composition in an inert gas, such as nitrogen, argon, or the like, prior to introducing the carrier or composition into the container. In still other examples, reducing a level of dissolved oxygen in the carrier can include bubbling the

carrier or composition with an inert gas, such as nitrogen, argon, or the like, at ambient or reduced atmospheric pressure prior to and/or during addition and mixing of L-cysteine. In some examples, reducing a level of dissolved oxygen in the carrier can be performed at an ambient or sub-ambient temperature. It is noted that the reduction of dissolved oxygen in the carrier to at or below a predetermined level can be accomplished without the addition of a supplementary antioxidant, but is not required in the methods and compositions described herein. Thus, the L-cysteine composition for injection is free of a supplementary antioxidant. As described elsewhere herein, attaining low and consistent dissolved oxygen was achieved using the protocol with sampling as set forth in Example 4.

The compositions have long-term stability. Thus, in certain embodiments, the amounts of the components described herein are amounts that are detected after the composition has been in storage. The compositions will have been stored at room temperature for less than a year, or for a year, or for more than a year. Such timelines include, for example, for about 15 months, for about 18 months, for about 24 months. Or, alternatively, the storage time could be for about 9 months, for about 7 months, for about 6 months, for about 5 months, for about 4 months, for about 3 months, for about 2 months, for about 1 month, or for about 3 weeks. Storage conditions are 25 ºC / 60% RH unless otherwise indicated.

Useful concentrations of L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof in a compositions as described herein include an amount from about 20 mg/mL to about 80 mg/mL, from about 30 mg/mL to about 70 mg/mL, from about 40 mg/mL to about 60 mg/mL, from about 45 mg/mL to about 55 mg/mL, or an amount of about 50 mg/mL, or from about 35 mg/mL to about 50 mg/mL, or an amount of about 37.5 mg/mL. It is noted that the amounts of L-cysteine disclosed herein, whether as a total mass or as a concentration, are based on L-cysteine hydrochloride monohydrate or the free base, as specified. Thus, where other forms of L-cysteine are employed in the composition, the amount of the alternative form included in the composition can be calculated based on an equivalent amount of L-cysteine hydrochloride monohydrate rather than the amount of the alternative form employed.

Thus, the stable L-cysteine composition can comprise total amounts of L-cysteine from about 200 mg to about 4000 mg, or from about 300 mg to about 700 mg, or from about 300 mg to about 400 mg. For example, a 10 mL vial could be manufactured to contain about 350 mg of L-Cysteine. In certain embodiments, the L-cysteine composition can comprise a total amount of L-cysteine from about 1200 mg to about 2000 mg. For example, a 50 mL container could be manufactured to contain about 1800 mg of L-Cysteine. In another embodiment, the total composition of an L-Cysteine composition container may range from about 3000 mg to about 4000 mg. For example, a 100 mL container could be manufactured to contain about 3500 mg of total L-Cysteine.

It has been found that the container in which the compositions are held can affect the level of certain components. In certain embodiments, the L-cysteine composition can be enclosed in a single-use container. The container can have a variety of volumes. Typically, the container can have a volume of from about 10 ml to about 100 ml. In some examples, the container can have a volume of from about 10 ml to about 50 ml. In other examples, the container can have a volume of from about 50 ml to about 100 ml. In still other examples, the container can have a volume of about 10 ml or about 20 ml.

The container can be made of a variety of materials. Non-limiting materials can include glass, a plastic (e.g. polyethylene, polypropylene, polyvinyl chloride, polycarbonate, etc.), the like, or a combination thereof provided that it can both prevent oxygen penetration and minimize Aluminum, heavy metals and anions contamination to the composition. Up to now, there has been no guidance with regard to the compatibility of L-cysteine with coated glass vials or that any vials could be used to provide L-cysteine compositions having low levels of Aluminum.

Another confounding factor is the low pH of the L-Cysteine product, which is less than 3.0 in certain embodiments. This low pH can disrupt the plastic coating or silicon coating inside the glass container and Aluminum, heavy metals and anions could leach during the shelf life of the product, especially over prolonged storage of the product. Therefore, up to now, the success of the product was uncertain until the products described

herein were manufactured and studied in real time for prolonged periods as described herein.

It should be recognized that vials which are impermeable with an internal coating, vials which are stored in a pouch that protects the product from atmospheric oxygen ingress, and relatively thick vials made of impermeable plastic or glass can be suitable for the L-Cysteine product disclosed herein.

Vials which are stored in a pouch can be prepared in a similar manner as described herein and then pouched in a plastic material that is then sealed. The pouch may be kept under vacuum or under an inert atmosphere. Methods for manufacturing such pouched products, and materials for such manufacture are known in the industry.

Relatively thick vials made of impermeable plastic are also prepared in a similar manner as described herein. Such vials may be composed of cyclic olefin materials of sufficient thickness to prevent oxygen ingress over a reasonably long period of time, for example 1 month, 2 months, 3 months, 6 months or 12 months. These vials are packaged and supplied as such. Alternatively, these vials can also be pouched as described above in plastic material that is kept under vacuum or under an inert gas atmosphere. It is expected that such pouching extends the shelf life of the product by at least 1 month, or 2 months, or 3 months, or 6 months or longer.

In certain embodiments, the vials are made of glass with an internal coating made of silicon dioxide, for example, Schott Type 1 Plus USP glass. The general thickness of the coating is presumed to be at least 100-200 nanometers thickness. It is believed that this level of thickness was sufficient to provide protection against pH disruption while also preventing the migration of Aluminum from the glass into the L-Cysteine product. Thus, in some specific examples, the container can be an internally coated glass container. In certain other embodiments the glass container is internally coated with silicon dioxide of about 100 to about 200 nanometers.

In certain embodiments the Aluminum contribution from the container may range from about 0.1 ppb to about 200 ppb. In certain other embodiments the Aluminum

contribution may range from about 1 ppb to about 150 ppb, from about 1 ppb to about 120 ppb, from about 1 ppb to about 100 ppb, from about 1 ppb to about 80 ppb, from about 1 ppb to about 60 ppb, from about 1 ppb to about 50 ppb, from about 1 ppb to about 40 ppb, from about 1 ppb to about 30 ppb, from about 1 ppb to about 25 ppb, from about 1 ppb to about 20 ppb, from about 1 ppb to about 15 ppb, from about 1 ppb to about 10 ppb, from about 1 ppb to 5 ppb. In certain embodiments, the contribution could be in subranges within the above ranges, for example, from about 35 to 55 ppb, or from about 75 to about 140 ppb, in increments of 5 ppb. All such ranges and subranges are contemplated herein.

The containers are sealed with a suitable stopper made of rubber, elastomeric polymers, or combinations thereof. In certain embodiments the stoppers are coated with a special non-reactive inert coating that minimizes interaction with drug product. For example, some stoppers are coated with Teflon to prevent drug-stopper interactions. One example of a specific coated stopper is supplied by West Pharma and is called V10-F597W Stopper, 20 mm Lyo, 4432/50 Gray, B2-TR Coating, Westar RS. This stopper is a cross-linked mixture of high- and low-molecular weight silicone oils that are cured through the application of UV rays and heat. Because it is a spray-on coating applied to molded closures before the trimming process, B2-Coating can be applied at various levels on the bottom and top of closures. These specific stoppers are preferred even though similar coating materials and methodology applied to other types of stoppers could also work. The stoppers are selected not only for their inertness vis-à-vis the drug product but also for their minimal contribution to Aluminum levels in the drug product.

In certain embodiments the Aluminum contribution from the stopper may range from about 0.1 ppb to about 100 ppb. In certain other embodiments the Aluminum contribution may range from about 1 ppb to about 90 ppb, from about 1 ppb to about 80 ppb, from about 1 ppb to about 70 ppb, from about 1 ppb to about 60 ppb, from about 1 ppb to about 50 ppb, from about 1 ppb to about 40 ppb, from about 1 ppb to about 30 ppb, from about 1 ppb to about 25 ppb, from about 1 ppb to about 20 ppb, from about 1 ppb to about 15 ppb, from about 1 ppb to about 10 ppb, from about 1 ppb to 5 ppb. In certain embodiments, the contribution could be in subranges within the above ranges, for example,

from about 35 to 55 ppb, or from about 25 to about 75 ppb, in increments of 5 ppb. All such ranges and subranges are contemplated herein.

In addition to the container and stopper, the drug substance and excipients including water for injection may contribute Aluminum to the drug product. Thus, in one aspect the Aluminum contribution from the drug substance may range from about 0.1 ppb to about 70 ppb. In certain other embodiments the Aluminum contribution may range from about 1 ppb to about 60 ppb, from about 1 ppb to about 50 ppb, from about 1 ppb to about 40 ppb, from about 1 ppb to about 30 ppb, from about 1 ppb to about 25 ppb, from about 1 ppb to about 20 ppb, from about 1 ppb to about 15 ppb, from about 1 ppb to about 10 ppb, from about 1 ppb to 5 ppb. In certain embodiments, the contribution could be in subranges within the above ranges, for example, from about 35 to 55 ppb, or from about 75 to about 140 ppb, in increments of 5 ppb. All such ranges and subranges are contemplated herein.

The water for injection may contribute Aluminum from about 0.1 ppb to about 20 ppb. In certain embodiments the Aluminum contribution may range from about 1 ppb to about 15 ppb, from about 1 ppb to about 12 ppb, from about 1 ppb to about 10 ppb, from about 1 ppb to about 8 ppb, from about 1 ppb to about 6 ppb, from about 1 ppb to about 5 ppb, from about 1 ppb to about 4 ppb, from about 1 ppb to about 3 ppb, from about 1 ppb to about 2.5 ppb, from about 1 ppb to about 2 ppb, from about 1 ppb to about 1.5 ppb. In certain embodiments, the contribution could be in subranges within the above ranges, for example, from about 5 to 7.5 ppb, or from about 10.5 to about 15.0 ppb, in increments of 0.5 ppb. All such ranges and subranges are contemplated herein.

In summary, to lower the Aluminum level to even greater extent as described herein, the container, the stopper, the drug substance, the water for injection, and any other excipients can be chosen such that the Aluminum concentration in the drug product is from about 1.0 ppb to about 250 ppb, or as described in the other embodiments provided herein.

Advantageously, in certain embodiments, the compositions maintain cystine levels for extended periods, and/or are substantially free or essentially free of cystine precipitate. However, it is noted that where cystine is present in the L-cysteine composition it is not

necessarily dissolved. For example, in some cases, it can be present in the composition as an undissolved particle.

Where the L-cysteine composition includes cystine, it can typically be present in relatively small amounts compared to L-cysteine. In certain embodiments, cystine is present in the composition in an amount not more than 2.0 wt% relative to L-cysteine after storage at ambient temperature for a period of 6 months. In certain embodiments, cystine is present in the composition in an amount not more than 1.0 wt% relative to L-cysteine after storage at ambient temperature for a period of 6 months. In certain embodiments, cystine is present in the composition in an amount not more than 0.5 wt% relative to L-cysteine after storage at ambient temperature for a period of 6 months. In certain embodiments, cystine is present in the composition in an amount not more than 0.4 wt% relative to L-cysteine after storage at ambient temperature for a period of 6 months. In certain embodiments, cystine is present in the composition in an amount not more than 0.3 wt% relative to L-cysteine after storage at ambient temperature for a period of 6 months. In certain embodiments, cystine is present in the composition in an amount not more than 0.2 wt% relative to L-cysteine after storage at ambient temperature for a period of 6 months. In certain embodiments, cystine is present in the composition in an amount not more than 0.1 wt% relative to L-cysteine after storage at ambient temperature for a period of 6 months.

Further, in certain embodiments, cystine can be present in the L-cysteine composition, but in an amount not more than 2.0 wt% relative to L-cysteine after storage at ambient temperature for a period of 3 months. In certain embodiments, cystine can be present in the L-cysteine composition, but in an amount not more than 2.0 wt% relative to L-cysteine after storage at ambient temperature for a period of 3 months. In some embodiments, cystine can be present in the L-cysteine composition in an amount from about 0.001 wt% to about 2.0 wt% relative to the amount of L-cysteine present in the composition. In some embodiments, cystine can be present in the L-cysteine composition in an amount from about 0.005 wt% to about 0.5 wt% relative to the amount of L-cysteine present in the composition. In some embodiments, cystine can be present in the L-cysteine

composition in an amount from about 0.05 wt% to about 1.0 wt% relative to the amount of L-cysteine present in the composition. In some embodiments, L-cystine can be present, but in an amount that is either not detectable or that is below a limit of quantitation using a standard testing procedure, such as a validated test method for detecting cystine.

Advantageously, in certain embodiments, the compositions maintain pyruvic acid levels for extended periods, and/or are substantially free or essentially free of pyruvic acid. When present, pyruvic acid is typically present in a relatively small amount compared to L-cysteine. In certain embodiments, pyruvic acid is present in the composition in an amount not more than 2.0 wt% relative to L-cysteine after storage at ambient temperature for a period of 6 months. In certain embodiments, pyruvic acid is present in the composition in an amount not more than 1.0 wt% relative to L-cysteine after storage at ambient temperature for a period of 6 months. In certain embodiments, pyruvic acid is present in the composition in an amount not more than 0.5 wt% relative to L-cysteine after storage at ambient temperature for a period of 6 months. In certain embodiments, pyruvic acid is present in the composition in an amount not more than 0.4 wt% relative to L-cysteine after storage at ambient temperature for a period of 6 months. In certain embodiments, pyruvic acid is present in the composition in an amount not more than 0.3 wt% relative to L-cysteine after storage at ambient temperature for a period of 6 months. In certain embodiments, pyruvic acid is present in the composition in an amount not more than 0.2 wt% relative to L-cysteine after storage at ambient temperature for a period of 6 months.

In certain embodiments, pyruvic acid is present in the composition in an amount not more than 0.1 wt% relative to L-cysteine after storage at ambient temperature for a period of 6 months. In certain embodiments, pyruvic acid can be present in the L-cysteine composition, but in an amount not more than 2.0 wt% relative to L-cysteine after storage at ambient temperature for a period of 3 months. In certain embodiments, pyruvic acid can be present in the L-cysteine composition, but in an amount not more than 2.0 wt% relative to L-cysteine after storage at ambient temperature for a period of 6 months. In some embodiments, pyruvic acid can be present in the L-cysteine composition in an amount from about 0.001 wt% to about 2.0 wt% relative to the amount of L-cysteine present in the

composition. In some embodiments, pyruvic acid can be present in the L-cysteine composition in an amount from about 0.005 wt% to about 0.5 wt% relative to the amount of L-cysteine present in the composition. In some embodiments, pyruvic acid can be present in the L-cysteine composition in an amount from about 0.05 wt% to about 1.0 wt% relative to the amount of L-cysteine present in the composition. In some embodiments, pyruvic acid can be present, but in an amount that is either not detectable or that is below a limit of quantitation using a standard testing procedure, such as a validated test method for detecting pyruvic acid.

As discussed above, to achieve safe method and compositions, it is beneficial to further understand which other components are present beyond Aluminum and pyruvic acid, and control their amounts as well. Because preterm infants could be exposed to L-Cysteine for potentially longer periods, and their main source of L-Cysteine is through parenteral administration, careful consideration should be given to exposure to other potentially unsafe compounds that may leach out of the container or stopper in amounts greater than what are considered safe limits. Examples include certain volatile compounds, certain heavy elements, and certain anions.

Daily acceptable limits are known for these potentially unsafe compounds. However, because the L-Cysteine Injection is used to infuse into preterm and term infants and those elderly that are critically ill will compromised renal functions, and sometimes for periods that exceed more than a few days, just meeting the daily acceptable limits may not be sufficient. Every effort must be made to reduce the levels to as low as practicable. The L-Cysteine compositions presented herein provide in some embodiments about one-half of the daily acceptable limits; in some embodiments, about one-fourth of the daily acceptable limits; in some embodiments, about one-fifth of the daily acceptable limits; in some embodiments, about one-sixth of the daily acceptable limits.

The anions that are desirable to control are: Iodide and Fluoride. The acceptable limit for Iodide is about 20 ppm or less. The acceptable limit for Fluoride is about 30 ppm or less. The L-Cysteine compositions provided herein show Iodide concentrations of less 20 ppm and Fluoride concentrations of less than 30 ppm when measured at any time from

the day of manufacture through its shelf-life of 6 months, or 12 months, or 18 months, or 24 months, when stored under Room Temperature Conditions. In some embodiments, the L-Cysteine compositions provide from about 1.0 ppm to 20 ppm of Iodide; in some embodiments, from about 1.0 ppm to about 15 ppm; in some embodiments, from about 1.0 ppm to about 10 ppm; and in some embodiments, from about 1.0 ppm to about 5 ppm. In some embodiments, the L-Cysteine compositions provide from about 1.0 ppm to 20 ppm of Fluoride; in some embodiments, from about 1.0 ppm to about 15 ppm; in some embodiments, from about 1.0 ppm to about 10 ppm; and in some embodiments, from about 1.0 ppm to about 5 ppm. Methods for evaluating the anions and the results are provided in Example 8.

As noted above, several elements may leach or be extracted out into the L-Cysteine drug product, thereby presenting a potential safety/toxicity concern to subjects that require L-Cysteine parenteral administration. Art-known methods may be used to evaluate the elemental levels. Inductively-coupled plasma mass spectral method is one such highly specific method. Example 9 provides the data generated by using ICP-MS technique. As shown in Example 9, there are over thirty elements that are generally known to present safety/toxicity concerns. The Table 22 provides the daily allowable limit for all of these elements, and the observed levels in the present L-Cysteine compositions. The daily allowable limit for some elements are relatively high, whereas for other elements they are relatively very low. For example, Molybdynum has the level of 14,500 ppb approximately, whereas Cadmium has about 19 ppb.

For purposes of monitoring the L-Cysteine compositions for the elements of concern, in one aspect, the levels of Mercury, Lead, Nickel and Arsenic are of significance. Therefore, in one aspect, the L-Cysteine compositions presented herein have further improved safety because they provide these elements at amounts far less than the daily allowable limits. Targeted daily allowable limits include 48 ppb for Lead, 29 ppb for Mercury, 194 ppb for Nickel, and 174 ppb for Arsenic.

The L-Cysteine compositions described herein provide from about 1 ppb to 10 ppb of Lead; in some embodiments, from about 1 ppb to about 8 ppb; in some embodiments,

from about 1 ppb to about 7 ppb; or in some embodiments, from about 1 ppb to about 5 ppb. when measured at any time from the day of manufacture through its shelf-life of 6 months, or 12 months, or 18 months, or 24 months, when stored under Room Temperature Conditions.

With respect to Mercury, the L-Cysteine compositions described herein provide from about 0.1 ppb to 10 ppb of Mercury; in some embodiments, from about 0.1 ppb to about 8 ppb; in some embodiments, from about 0.1 ppb to about 7 ppb; or in some embodiments, from about 0.1 ppb to about 5 ppb. when measured at any time from the day of manufacture through its shelf-life of 6 months, or 12 months, or 18 months, or 24 months, when stored under Room Temperature Conditions.

With respect to Nickel, the L-Cysteine compositions described herein provide from about 1 ppb to 50 ppb of Nickel; in some embodiments, from about 1 ppb to about 40 ppb; in some embodiments, from about 1 ppb to about 30 ppb; or in some embodiments, from about 1 ppb to about 25 ppb; or in some embodiments from about 1 ppb to about 20 ppb, when measured at any time from the day of manufacture through its shelf-life of 6 months, or 12 months, or 18 months, or 24 months, when stored under Room Temperature Conditions.

With respect to Arsenic, the L-Cysteine compositions described herein provide from about 0.1 ppb to 60 ppb of Arsenic; in some embodiments, from about 0.1 ppb to about 50 ppb; in some embodiments, from about 0.1 ppb to about 40 ppb; in some embodiments, from about 0.1 ppb to about 30 ppb; in some embodiments, from about 0.1 ppb to about 25 ppb; or in some embodiments from about 0.1 ppb to about 20 ppb; in some embodiments, from about 0.1 ppb to about 15 ppb; in some embodiments, from about 0.1 ppb to about 10 ppb; or in some embodiments, from about 0.1 ppb to about 5.0 ppb, when measured at any time from the day of manufacture through its shelf-life of 6 months, or 12 months, or 18 months, or 24 months, when stored under Room Temperature Conditions.

In some embodiments, the Arsenic, Mercury, Lead and other elements may be extracted from the container or from the stopper. In one specific embodiment, the extracted out amount of Arsenic, Mercury, Lead, and Nickel combined from the stopper is 100 ppb

or less. In other embodiments, the extracted amount of Arsenic, Mercury, Lead, and Nickel combined from the stopper is from about 10 to about 50 or from about 10 to about 100 ppb.

It should be recognized that in some instances the amount of a specific element present in the L-Cysteine compositions described herein may be below the Limit of Quantitation (LOQ). In those instances, for purposes of this disclosure and claims made herein, the compositions may be considered to contain the lowest level described in the preceding paragraphs. For example, when Arsenic is determined to be below the LOQ, the Arsenic amount may be considered to be at 0.1 ppb. Therefore, all such instances where the compositions show amounts below the LOQ are within the contemplation of this disclosure.

In certain embodiments, the compositions further comprise within the container, headspace gas that includes oxygen in an amount of from about 0.5% v/v to about 5.0 % v/v, or from about 0.5% v/v to about 4.0% v/v, or from about 0.5% v/v to about 3.5% v/v, from about 0.5% v/v to about 3.0 % v/v, or from about 0.5% v/v to about 2.5% v/v, or from about 0.5% v/v to about 2.0 % v/v, or from about 0.5% v/v to about 1.5% v/v, or from about 0.5% v/v to about 1.0 % v/v, or in some cases from about 0.1% v/v to about 0.5% v/v, or from about 0.1% v/v to about 0.4% v/v, or from about 0.1% v/v to about 0.3% v/v, or from about 0.1% v/v to about 0.2% v/v. For the sake of clarity and the ease of discussion and measurement, these values are taken for the L-Cysteine composition at the time of its manufacture ("tine zero" data point), or during and up to 1 month from time zero. Additional time points beyond the 1-month from time zero data point may provide similar headspace oxygen levels.

Without wishing to be bound by theory, the dissolved oxygen levels and the head space oxygen levels within a sealed container of L-Cysteine compositions described herein may reach an equilibrium at some time point during its shelf-life. Such equilibrium may be maintained for a very short time, i.e., for a few seconds, or for a very long time, i.e., for several months. Such equilibrium may on occasion be disturbed by simple agitation. Therefore, it should be recognized that dissolved oxygen levels and headspace oxygen levels may fluctuate from one time point to another in terms of absolute numbers. However,

the numbers are expected to stay within the ranges disclosed herein. Occasionally, one number (e.g., dissolved oxygen) may exceed or fall out of a certain range (e.g., from about 05 to about 3.0 PPM) at a 15-day time point, but may fall within that range at some other time point (e.g., 30 day time point, or later). Therefore, in some aspects, the ranges, subranges, and specific data points disclosed and discussed herein are valid and suitable for time points beyond the time zero and 1-month time points. In one aspect, the time points could be extended to 2-months, 3-months, 6-months, 9-months, 12-months, 15-months, 18-months, and 24 months.

In some aspects, the total amount of oxygen in the sealed container may be an appropriate measure to evaluate the stability of the L-Cysteine compositions herein. For example, the total amount of oxygen within the container may be arrived at by adding up the amount of dissolved oxygen in the carrier and the amount of head space oxygen. These values can also be expressed independently in separate units (i.e., dissolved oxygen as ppm and head space oxygen as % v/v). An example would be an L-Cysteine composition that contains a dissolved oxygen level of from about 0.1 ppm to 4.0 ppm and a head space oxygen level of about 0.5% v/v to about 4.0% v/v.

The amount of oxygen present in the headspace of the container can be controlled by filling the headspace with an inert gas, such as nitrogen or argon. Alternatively, the head space oxygen may be controlled by vacuum operation without using an inert gas. In another aspect, the head space oxygen may be controlled by a combination of vacuum operation and inert gas overlay. In one particular aspect, the head space oxygen is controlled by repeated pulses of vacuum and inert gas overlay in tandem such that the process may start first with vacuum operation followed by inert gas overlay followed by vacuum operation. The combination of vacuum operation and inert gas overlay (or inert gas overlay and vacuum operation) is considered one pulse when both steps are used together. A typical head space control operation may comprise from one to eight pulses. Typically, there could be two, three, four, or five pulses. Each pulse could last from about one tenth of one second to five seconds or from five to fifteen seconds when conducted by automated high-speed equipment custom designed for this specific purpose. In some

embodiments, the pulse may last from about 0.1 to about 2.0 seconds. In some embodiments, the pulse may last from about 0.1 to about 1.0 seconds, or from about 0.1 to about 0.4 seconds. When done using manual methods, each pulse could take up to 30-60 seconds or longer. Such a manual process is described in more detail in Examples 1 and 4. Alternatively, a more automated process that was developed by the current inventors is described in Example 5.

In certain embodiments, the compositions are part of a total parenteral nutrition regimen. The L-cysteine compositions described herein can be admixed with amino acid solutions, such as crystalline amino acid injection, for example, commercially available TRAVASOL® and TRAVASOL E®.

In certain aspects, the subject matter described herein is directed to a safe, stable composition from about 100 mL to about 1000 mL for administration via a parenteral infusion within about 24 to about 48 hours of admixture, comprising a mixture of a composition of L-Cysteine described herein; and an amino acid composition that is essentially free of L-Cysteine comprising one or more amino acids selected from the group consisting of: leucine, isoleucine, lysine, valine, phenylalanine, histidine, threonine, methionine, tryptophan, alanine, arginine, glycine, proline, serine, and tyrosine.

In certain embodiments, the subject matter described herein is directed to a stable TPN composition for infusion, comprising:

L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof;

Aluminum in an amount from about 10 parts per billion (ppb) to about 80 ppb;

cystine in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine;

pyruvic acid in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine;

one or more amino acids selected from the group consisting of: leucine, isoleucine, lysine, valine, phenylalanine, histidine, threonine, methionine, tryptophan, alanine, arginine, glycine, proline, serine, and tyrosine;

a pharmaceutically acceptable carrier, comprising water,

wherein, the amounts are from about 100 mL to about 1,000 mL and the total aluminum delivered by the said composition does not exceed about 4-5 mcg/kg/day. In certain embodiments, the amounts include 150 mL, 200 mL, 250 mL, 300 mL, 350 mL, 400 mL, 450 mL, 500 mL, 550 mL, 600 mL, 650 mL, 700 mL, 750 mL, 800 mL, 850 mL, 900 mL and 950 mL.

In certain embodiments, the stable composition for infusion comprises one or more amino acids selected from the group consisting of leucine, isoleucine, lysine, valine, phenylalanine, histidine, threonine, methionine, tryptophan, alanine, arginine, glycine, proline, serine, and tyrosine. In certain embodiments, the composition includes all of these. In certain embodiments, 500 mg of L-Cysteine is admixed with 12.5 gram of crystalline amino acid injection, such as that present in 250 mL of 5% crystalline amino acid injection. In some aspects, 15 mg of L-Cysteine is admixed with one gram of amino acids. In some other aspect, 40 mg of L-Cysteine is admixed with one gram of amino acids. Depending on the needs of the subject, based on specific characteristics such as age, weight, and physiological factors such as renal function, the dose may be adjusted at or within these ranges of 15-40 mg of L-Cysteine per gram of amino acids. See, for example, Tables 1-2 above. Thus, the pharmaceutical compositions comprising L-Cysteine can be formulated, dosed and administered in a fashion, *i.e.*, amounts, concentrations, schedules, course, and vehicles, consistent with good medical practice. The "therapeutically and nutritionally effective amount" of the compound to be administered will be governed by such considerations.

In certain embodiments, the compositions are essentially free of supplementary antioxidant. As used herein, this refers to the absence of any substance that is added to the compositions specifically as an antioxidant. Naturally occurring antioxidants may still be present.

In certain embodiments, the compositions that comprise one or more of the above amino acids are essentially free of dextrose. However, in certain embodiments, the compositions that comprise one or more of the above amino acids further comprise a sugar.

In certain embodiments, the pH of the compositions is about 1.0 to about 2.5, or about 1.6 to about 2.0, or about 1.6, or about 1.7, or about 1.8, or about 1.9 or about 2.0. For administration, the pH is generally adjusted by admixing with other components to a pH of about 6.0 to about 8.0, but generally around 7.0. In certain embodiments, the compositions are essentially free of a buffer. In certain embodiments, the compositions further comprise a buffer.

In particular embodiments, the subject matter described herein is directed to a stable L-cysteine composition for injection that can be useful for treatment of a variety of conditions, such as those described above. In further detail, L-cysteine can be administered in a variety of forms, such as the free base, L-cysteine hydrochloride, a pharmaceutically acceptable salt thereof (e.g. sodium salt, calcium salt, etc.), a hydrate thereof, the like, or a combination thereof. In some specific examples, L-cysteine can be included in the L-cysteine composition for injection as L-cysteine hydrochloride monohydrate.

In particular embodiments, the subject matter described herein is directed to a stable L-cysteine composition for injection, comprising:

about 34.5 mg/mL of L-cysteine free base, or a pharmaceutically acceptable salt thereof and/or hydrate thereof;

Aluminum in an amount of 130 ppb or below;

water;

wherein the composition is enclosed in a single-use container having a volume of from 10 mL to 100 mL, and is stable for 9 months or less.

In certain embodiments, the stable, safe L-cysteine composition can consist essentially of L-cysteine, water, Aluminum in an amount of less than 200 ppb, cystine in an amount from about 0.001 wt% to about 2 wt% relative to L-cysteine, pyruvic acid in an amount from about 0.001 wt% to about 2 wt% to L-cysteine, headspace oxygen that is less than 4.0% and dissolved oxygen from about 0.1 ppm to about 1 ppm. Other trace components or excipients do not materially affect the basic and novel characteristics of composition unless otherwise indicated, for example, undesirable anions and heavy metals.

The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings, more specifically about the Aluminum content of the L-Cysteine composition. For example, the label may indicate that the Aluminum in the container may be at 100 ppb or 100 mcg/L. In another embodiment, the label may indicate that the Aluminum in the container may be at 120 ppb or 120 mcg/L. In some specific embodiments, the Aluminum level may be described as not more than 120 ppb, or not more than 120 mcg/L, or NMT 120 ppb, or NMT 120 mcg/L. In addition to the label, the labeling associated with the L-Cysteine product may have the same description of Aluminum.

It should be understood that, as is customary in the pharmaceutical arts, the phrases "NMT" or "not more than" represents the upper limit, but also is understood not to mean that the value is zero or even can be zero. For example, a statement that the Aluminum levels are NMT 120 ppb is not understood by the practitioners in the art that the Aluminum levels are at zero ppb in that particular vial bearing that label. Pharmacists and other health care professionals instead would interpret for purposes of calculating the Aluminum content of a TPN preparation using that specific L-Cysteine vial that the Aluminum levels are at 120 ppb so that, even if the actual amount is lower than the 120 ppb in the product, they err on the conservative side. This is the custom in the pharmaceutical industry developed and practiced to safeguard the health of patients. If indeed the label is intended to convey with certainty that the actual Aluminum level is zero ppb, the label then would state that fact or indicate that the product is free of Aluminum.

Similarly, any numerical value expressed as "less than" is intended to convey that the value is below that certain numerical value, including, as the case may be zero. For example, when it is stated herein that Aluminum levels are less than about 20 ppb, it is

understood that in some embodiments the Aluminum can be, but not necessarily in all cases, anywhere from zero to about 19 ppb. It is also understood that this may, but not necessarily in all cases, encompass those situations where the levels are below quantitation limit, but the presence of Aluminum is detectable. In those cases where the Aluminum (or any other measured material generally) where the material is detectable but is below the level of quantitation, that numerical value can be considered for example as being about 1.0 (for Aluminum) or 0.001 (for Cystine or Pyruvic acid), or 1.0 ppb (for elements) or 1.0 ppm (for iodide or fluoride). Unless an actual analysis is made of the product and a specific number is determined, there is no certainty of the actual value. The US FDA does not require this precision in the labeling on a product-by-product or even batch-by-batch because that is impracticable in a commercial supply chain setting for drug products.

Thus, the phrases "NMT" or "not more than" or "less than" are terms of art in the pharmaceutical industry. Those in the industry do not assume these terms necessarily represent zero in all cases, even though that is a possibility. When calculating the Aluminum amounts for purposes of preparing parenteral nutrition products the artisan never assumes the Aluminum levels are zero in order to safeguard the patient health. Accordingly, this present disclosure and the claims derived therefrom are to be read and understood in light of this custom and practice in the art.

As mentioned above, the L-cysteine compositions for infusion may optionally be mixed with pharmaceutically acceptable excipients, also described in *Remington's Pharmaceutical Sciences* (1980) 16$^{th}$ edition, Osol, A. Ed., Mack Publishing Co., Easton, PA.

As noted above, the diluted L-cysteine composition for infusion can typically have a pH of from about 5.0 to about 8.0, or from about 6.0 to about 7.0. However, dilution and administration of the L-cysteine composition for infusion will typically be overseen by a licensed medical professional, who may recommend a pH outside of the ranges recited herein under certain circumstances. Additionally, the diluted L-cysteine composition for infusion can typically have a tonicity of from about 250 milliosmoles/liter (mOsmol/L) to about 1,000 mOsmol/L, or more, or of from about 350 mOsmol/L to about 475 mOsmol/L.

However, dilution and administration of the L-cysteine composition for infusion will typically be overseen by a licensed medical professional, who may recommend a tonicity outside of the ranges recited herein under certain circumstances.

III. Methods

The subject matter described herein is directed to methods of treating a subject having an adverse health condition that is responsive to L-cysteine administration. The methods can include diluting the stable L-cysteine composition described herein with an intravenous fluid to prepare a diluted L-cysteine composition for infusion. The methods can further include parenterally administering the diluted L-cysteine composition to provide a therapeutically effective dose of L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof to the subject in a therapeutically effective dosing regimen.

In certain embodiments, the subject matter described herein is directed to a method of reducing Aluminum administration from a total parenteral nutrition regimen comprising L-cysteine, the method comprising, mixing a composition comprising L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof comprising:

Aluminum in an amount from about 1.0 parts per billion (ppb) to about 250 ppb or from about 10 ppb to about 80 ppb;

L-cystine in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine; and

pyruvic acid in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine;

with a composition comprising one or more amino acids selected from the group consisting of: leucine, isoleucine, lysine, valine, phenylalanine, histidine, threonine, methionine, tryptophan, alanine, arginine, glycine, proline, serine, and tyrosine; and

a pharmaceutically acceptable carrier, comprising water,

to form a composition for infusion of about 100 mL to about 1000 mL,

wherein the Aluminum provided in said parenteral nutrition regimen is from about 1-2 to about 4-5 micrograms/kg/day.

In certain aspects, the compositions and methods described herein are directed to methods of administering L-Cysteine together with a composition for parenteral nutrition, comprising:

diluting a stable L-cysteine composition for injection as described herein with a parenteral nutrition composition to form a mixture; and

parenterally administering the mixture to a subject in need thereof in a therapeutically and/or nutritionally effective dose. In one aspect, the subject is a neonatal weighing less than 2 kilos. In another aspect, the subject is a pediatric patient that is from about 0.2 kilos to about 20 kilos. In another aspect, the subject is an adult requiring parenteral nutrition.

In certain embodiments, the subject matter described herein is directed to a method of reducing Aluminum administration from a parenteral nutrition regimen comprising L-cysteine, comprising:

administering to a subject a composition comprising L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof;

Aluminum in an amount from about 10.0 parts per billion (ppb) to about 250 ppb, or from about 10 ppb to about 80 ppb;

cystine in an amount from about 0.01 wt% to about 2.0 wt% relative to L-cysteine;

pyruvic acid in an amount from about 0.01 wt% to about 2.0 wt% relative to L-cysteine;

one or more amino acids selected from the group consisting of: leucine, isoleucine, lysine, valine, phenylalanine, histidine, threonine, methionine, tryptophan, alanine, arginine, glycine, proline, serine, and tyrosine,

a pharmaceutically acceptable carrier, comprising water,

wherein, the amounts are about 100 mL to about 1,000 mL,

wherein the Aluminum administered to said subject is reduced compared to administration of a standard parenteral composition comprising L-cysteine and Aluminum at a range of from about 900 ppb to about 5,000 ppb.

In certain embodiments, the methods provide that the reduction in the amount of Aluminum administered is relative to the amount of Aluminum in a L-cysteine injection composition having more than 500 ppb Aluminum, or more than 250 ppb Aluminum. The relative reduction in Aluminum can be up to 90%, up to 80%, up to 70%, up to 60%, up to 50%, up to 40%, up to 30%, up to 20%, up to 10%, or up to 5%, as compared to the amount of Aluminum administered with a L-cysteine composition having more than 500 ppb Aluminum, or more than 250 ppb Aluminum. In certain embodiments, the reduction occurs over the span of a day, a week, a month or the duration of the TPN regimen.

In certain aspects, the subject matter described herein is directed to methods of treating a subject having an adverse health condition that is responsive to L-cysteine administration, comprising:

diluting a stable L-cysteine composition as described herein with an intravenous fluid to prepare a diluted L-cysteine composition for infusion; and

infusing the diluted L-cysteine composition for infusion to a subject to provide a therapeutically effective dose of L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof to the subject in a therapeutically effective dosing regimen.

In certain embodiments, the method of treating a subject having an adverse health condition that is responsive to L-cysteine administration further comprises, before the diluting step, admixing the stable L-cysteine composition with an amino acid solution, such as, crystalline amino acid injection. In this aspect, the methods comprise diluting with an intravenous fluid the stable L-cysteine composition admixed with an amino acid solution, wherein the fluid comprises dextrose.

In certain embodiments, the adverse health condition is the lack of a necessary enzyme in the trans-sulfuration pathway that converts methionine to L-cysteine. Other adverse health conditions include inadequate absorption resulting from short bowel syndrome; gastrointestinal fistula; bowel obstruction; prolonged bowel rest; severe malnutrition; significant weight loss and/or hypoproteinaemia when enteral therapy is not possible; other disease states or conditions in which oral or enteral feeding are not an option.

For most preterm infants, the administration should be considered as a short-term bridge to provide nutritional support until full enteral nutrition can be provided. Such instances include: Immediately after birth, to provide essential nutrition as enteral feeds are commenced and advanced, and/or during periods of acute gastrointestinal malfunction (eg, due to septic ileus or necrotizing enterocolitis).

In certain embodiments, the administering is a single daily dose, or multiple daily doses, or is administered in accordance with a TPN regimen, for example, the dosing can be over a day, several days, a week or several weeks, a month or several months.

In certain embodiments, the subject is an infant or pre-term infant from newborn until about 6 months of age. As presented in Tables 1 and 2 above, the subjects can be from a pre-term infant to an adult that is in need of L-Cysteine supplementation. Thus, the subject can be a subject "in need of" the methods of described herein, for example, in need of the therapeutic effects or prophylactic benefits of the methods. In certain embodiments, the subject is a subject in need of a total parenteral nutrition (TPN) regimen.

In certain embodiments, the intravenous fluid is selected from the group consisting of isotonic saline, glucose solution, glucose saline, dextrose solution, crystalline amino acid solution, lipids, and combinations thereof.

In certain embodiments, the L-cysteine is L-cysteine hydrochloride monohydrate.

In certain embodiments, the diluted L-cysteine composition for infusion is typically administered via intravenous infusion. The selection of administration rate and site of infusion (i.e., via a peripheral or central vein) are within the ordinary skill in the art of medicine, pharmaceutical, nursing, and nutritional sciences.

The diluted L-cysteine composition for infusion can be administered until a therapeutically effective dose is achieved. In some examples, a therapeutically effective dose of L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof can be from about 0.01 mg to about 2.0 mg L-cysteine. Again, therapeutically effective doses can depend on whether the patient is a pediatric patient or an adult patient. For example, for preterm or term infants less than 1 month of age, the therapeutically effective dose is

about 45 to 60 mcg/kg/day. For pediatric patients 1 month to less than 1 year of age, the therapeutically effective dose is 30 to 45 mcg/kg/day. For pediatric patients 1 year to 11 years of age, the therapeutically effective dose is about 15 to 30 mcg/kg/day. For pediatric patients 12 years to 17 years of age, the therapeutically effective dose is about 4 to 7.5 mcg/kg/day. For adults, i.e., stable patients, the therapeutically effective dose is 4 to 5 mcg/kg/day. For adults that are critically ill, the therapeutically effective dose is 7.5 to 10 mcg/kg/day.

The number of doses given daily can vary as desired or needed per the therapeutically effective dosing regimen. In some examples, the therapeutically effective dosing regimen can include daily administration of the diluted L-cysteine composition. In other examples, the therapeutically effective dosing regimen can include twice-daily administration of the diluted L-cysteine composition. In some further examples, the therapeutically effective dosing regimen can provide less than or equal to 5 µg/kg/d of Aluminum. In still further examples, the therapeutically effective dosing regimen can provide less than or equal to 4 µg/kg/d of Aluminum, or less than or equal to 3 µg/kg/d of Aluminum. In certain embodiments, the methods result in a daily dosage of Aluminum from the composition of from about 2 µg/kg/d to not more than 5 µg/kg/d.

The diluted L-cysteine composition for infusion can be administered for the treatment of a number of conditions. For example, L-cysteine can be administered to meet the intravenous amino acid nutritional requirements of individuals (e.g. infants) receiving total parenteral nutrition. As such, in some examples, the subject can be a subject in need of total parenteral nutrition (TPN). In some additional examples, L-cysteine can be administered for the treatment of osteoarthritis, rheumatoid arthritis, angina, chronic bronchitis, chronic obstructive pulmonary disease (COPD), influenza, acute respiratory distress syndrome (ARDS), diabetes (e.g. type 2 diabetes), the like, or a combination thereof.

In certain embodiments, the subject matter described herein is directed to methods of preparing a composition, comprising:

Stirring Water for Injection, USP (WFI) in a vessel at a temperature of NMT about 60°C;

Contacting the stirring WFI with Argon until the dissolved oxygen is NMT 1 ppm;

Allowing the vessel to cool to a temperature of NMT 30°C;

Contacting under the Argon the WFI with L-Cysteine Hydrochloride, Monohydrate, USP (L-Cysteine) for NLT about 15 mins;

Continuing the mixing under Argon until the dissolved oxygen is NMT 1 ppm;

Adjusting the pH to about 1.8 with concentrated Hydrochloric Acid, NF and/or 5.0 N Sodium Hydroxide, NF;

Mixing for a minimum of about 10 minutes;

Capping the vessel under Argon and allowing to stand;

Filling said mixed liquid into individual single use containers;

Reducing head space oxygen to about 5.0% to 0.5% and sealing said containers wherein the dissolved oxygen in the container is about 0.1 ppm to about 5 ppm.

The subject matter described herein includes, but is not limited to, the following specific embodiments:

1. A stable L-cysteine composition for parenteral administration, comprising:

L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof in an amount from about 10 mg/mL to about 100 mg/mL;

Aluminum (Al) in an amount from about 1.0 parts per billion (ppb) to about 250 ppb;

L-cystine in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine;

pyruvic acid in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine;

a pharmaceutically acceptable carrier, comprising water;

headspace $O_2$ that is from about 0.5% to 4.0% from the time of manufacture to about 1 month from manufacture when stored at room temperature;

dissolved oxygen present in the carrier in an amount from about 0.1 parts per million (ppm) to about 5 ppm from the time of manufacture to about 1 month from manufacture when stored at room temperature,

wherein the composition is enclosed in a single-use container having a volume of from about 10 mL to about 100 mL.

2. The composition of embodiment 1, wherein the composition is essentially free of an antioxidant.

3. The composition of embodiment 1 or 2, wherein said Aluminum is present in an amount from about 1.0 ppb to about 200 ppb.

4. The composition of embodiment 1, 2 or 3, wherein said Aluminum is present in an amount from about 1.0 ppb to about 180 ppb.

5. The composition of embodiment 1, 2, 3 or 4, wherein said Aluminum is present in an amount from about 1.0 ppb to about 170 ppb.

6. The composition of embodiment 1, 2, 3, or 5, wherein said Aluminum is present in an amount from about 1.0 ppb to about 160 ppb.

7. The composition of embodiment 1, 2, 3, 4, 5 or 6, wherein said Aluminum is present in an amount from about 1.0 ppb to about 150 ppb.

8. The composition of embodiment 1, 2, 3, 4, 5, 6 or 7, wherein said Aluminum is present in an amount from about 1.0 ppb to about 130 ppb.

9. The composition of embodiment 1, 2, 3, 4, 5, 6, 7 or 8, wherein said Aluminum is present in an amount from about 1.0 ppb to about 100 ppb.

10. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, wherein said Aluminum is present in an amount from about 1.0 ppb to about 50 ppb.

11. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11, wherein said Aluminum is present in an amount from about 1.0 ppb to about 20 ppb or from about 1.0 ppb to about 10 ppb.

12. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11, further comprising one or more heavy metals selected from the group consisting of Lead (in an amount of from about 1 ppb to about 10 ppb), Nickel (in an amount of from about 5 ppb to about 40

ppb), Arsenic (in an amount of from about 0.1 ppb to about 10 ppb), and Mercury (in an amount of from about 0.2 ppb to about 5.0 ppb).

13. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, wherein said heavy metals are present in total in an amount from about 2.0 ppb to about 8.0 ppb.

14. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, further comprising iodide and fluoride, each present in an amount from about 0.1 ppm to about 20 ppm.

15. The composition of embodiment 14, wherein said ions are present in total an amount from about 2.8 ppm to about 5.8 ppm.

16. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, wherein said dissolved oxygen is present in an amount from about 0.1 ppm to about 5 ppm.

17. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, wherein said dissolved oxygen is present in an amount from about 0.1 ppm to about 3 ppm.

18. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17, wherein said dissolved oxygen is present in an amount from about 0.10 ppm to about 2.0 ppm.

19. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18, wherein said dissolved oxygen is present in an amount from about 0.1 ppm to about 1.0 ppm.

20. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or 19, wherein the composition has been stored at room temperature.

21. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, wherein the storage is for 1 year or less.

22. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21, wherein the storage is for about 9 months.

23. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or 22, wherein L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof is present in the composition in an amount from about 20 mg/mL to about 70 mg/mL.

24. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 or 23, wherein L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof is present in the composition in an amount of about 50 mg/mL.

25. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24, wherein the container is an internally coated glass container.

26. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25, wherein said internally coated glass container is coated with SiO2.

27. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or 26, essentially free of cystine precipitate.

28. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26 or 27, wherein said L-cysteine is present in an amount of about 37.5 mg/mL as free base, or a pharmaceutically acceptable salt thereof and/or hydrate thereof.

29. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, wherein the Aluminum is present in the composition in an amount not more than 200 ppb after storage at ambient temperature for a period of 3 months or less, said Aluminum comprising, from about 1.0 ppb to about 100 ppb of Aluminum from the container, from about 1.0 ppb to about 100 ppb of Aluminum from stopper for the container, from about 1.0 ppb to about 100 ppm of Aluminum from the L-cysteine, and from about1. 0 ppb to about 20 ppb of Aluminum from the water.

30. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, wherein the Aluminum is present in the composition in an amount not more than 200 ppb after storage at ambient temperature for a period of 6 months or less, said Aluminum comprising, from about 0 ppb to about 100 ppb of Aluminum from the container, from about 1.0 ppb to about 100 ppb of Aluminum from stopper for the container, from about 1.0 ppb to about 100 ppm of Aluminum from the L-cysteine, and from about 0 ppb to about 20 ppb of Aluminum from the water.

31. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, wherein the Aluminum is present in the composition in an amount not more than 200 ppb after storage at ambient temperature for a period of 9 months or less, said Aluminum comprising, from about 1.0 ppb to about 100 ppb of Aluminum from the container, from about 1.0 ppb to about 100 ppb of Aluminum from stopper for the container, from about 1.0 ppb to about 100 ppm of Aluminum from the L-cysteine, and from about 1.0 ppb to about 20 ppb of Aluminum from the water.

32. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, wherein the Aluminum is present in the composition in an amount not more than 200 ppb after storage at ambient temperature for a period of 12 months or less, said Aluminum comprising, from about 1.0 ppb to about 100 ppb of Aluminum from the container, from about 1.0 ppb to about 100 ppb of Aluminum from stopper for the container, from about 1.0 ppb to about 100 ppm of Aluminum from the L-cysteine, and from about 1.0 ppb to about 20 ppb of Aluminum from the water.

33. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, wherein cystine is present in the composition in an amount not more than 2 wt% relative to L-cysteine after storage at ambient temperature for a period of 9 months or less.

34. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, wherein cystine is present in the composition in an amount not more than 1 wt% relative to L-cysteine after storage at ambient temperature for a period of 9 months or less.

35. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, wherein cystine is present in the composition in an amount not more than 0.5 wt% relative to L-cysteine after storage at ambient temperature for a period of 9 months or less.

36. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, wherein cystine is present in the composition in an amount of about 0.3 wt% relative to L-cysteine after storage at ambient temperature for a period of 9 about months.

37. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, wherein pyruvic acid is present in the composition in an amount not more than 2 wt% relative to L-cysteine after storage at ambient temperature for a period of 9 months or less.

38. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, wherein pyruvic acid is present in the composition in an amount not more than 1 wt% relative to L-cysteine after storage at ambient temperature for a period of 9 months or less.

39. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, wherein pyruvic acid is present in the composition in an amount not more than 0.5 wt% relative to L-cysteine after storage at ambient temperature for a period of 9 months or less.

40. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, wherein pyruvic acid is present in the composition in an amount not more than 0.3 wt% relative to L-cysteine after storage at ambient temperature for a period of 9 months or less.

41. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, wherein pyruvic acid is present in the composition in an amount not more than 0.2 wt% relative to L-cysteine after storage at ambient temperature for a period of 9 months or less.

42. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, wherein pyruvic acid is present in the composition in an amount not more than 0.1 wt% relative to L-cysteine after storage at ambient temperature for a period of 9 months or less.

43. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, further comprising in the vial, headspace oxygen in an amount of less than 1.0%.

44. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, further comprising in the vial, headspace oxygen in an amount of less than 0.9%.

45. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, further comprising in the vial, headspace oxygen in an amount of less than 0.8%.

46. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, further comprising in the vial, headspace oxygen in an amount of less than 0.6%.

47. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, further comprising in the vial, headspace oxygen in an amount of less than 0.4%.

48. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, further comprising in the vial, headspace oxygen in an amount of less than 0.2%.

49. The composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, wherein the pH of the composition is about 1.6 to about 2.0.

50. A stable composition from about 100 mL to about 1000 mL for administration via a parenteral infusion within about 24 to about 48 hours of admixture, comprising a mixture of a composition of L-Cysteine of embodiments 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48 or 49; and an amino acid composition that is essentially free of L-Cysteine comprising one or more amino acids selected from the group consisting of: leucine, isoleucine, lysine, valine, phenylalanine, histidine, threonine, methionine, tryptophan, alanine, arginine, glycine, proline, serine, and tyrosine.

51. The stable composition for infusion of embodiment 50, wherein the composition of L-Cysteine is the composition of embodiment 1, 12 or 28.

52. The stable composition for injection of embodiment 50 or 51, wherein the Aluminum is present in an amount from about 1.0 parts per billion (ppb) to about 100 ppb.

53. The stable composition for injection of embodiment 50, 51 or 52, wherein the Aluminum is present in an amount from about 1.0 parts per billion (ppb) to about 50.0 ppb.

54. The stable composition for injection of embodiment 50, 51, 52 or 53, wherein the Aluminum is present in an amount from about 1.0 parts per billion (ppb) to about 30.0 ppb.

55. The stable composition for injection of embodiment 50, 51, 52, 53 or 54, further comprising a sugar.

56. The stable composition for injection of embodiment 50, 51, 52, 53, 54 or 55, wherein the sugar is dextrose.

57. A method of reducing Aluminum administration from a parenteral nutrition regimen comprising L-cysteine, comprising:

administering to a subject a composition of embodiment 50, 51, 52, 53, 54, 55 or 56,

wherein the Aluminum administered to said subject is reduced compared to administration of a standard parenteral composition comprising L-cysteine.

58. The method of embodiment 57, wherein the Aluminum is reduced by about 5%, or about 10%, or about 15%, or about 20%, or about 25%, or about 30%, or about 35%, or about 40%, or about 45%, or about 50%, or about 55%, or about 60%, or about 65%, or about 70%, or about 75%, or about 80%, or about 85%, or about 90%, or about 95%.

59. A method of reducing Aluminum administration from a total parenteral nutrition regimen comprising L-cysteine, the method comprising, mixing a composition comprising L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof comprising:

Aluminum in an amount from about 10 parts per billion (ppb) to about 80 ppb;

L-cystine in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine; and

pyruvic acid in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine;

with a composition comprising one or more amino acids selected from the group consisting of: leucine, isoleucine, lysine, valine, phenylalanine, histidine, threonine, methionine, tryptophan, alanine, arginine, glycine, proline, serine, and tyrosine; and

a pharmaceutically acceptable carrier, comprising water,

to form a composition for infusion having a volume of about 100 mL to about 1000 mL,

wherein the Aluminum provided in said parenteral nutrition regimen is from about 1-2 to about 4-5 micrograms/kg/day.

60. A method of treating a subject having an adverse health condition that is responsive to L-cysteine administration, comprising:

diluting a stable L-cysteine composition of embodiments 50, 51, 52, 53, 54, 55 or 56, with an intravenous fluid to prepare a diluted L-cysteine composition for infusion; and

infusing the diluted L-cysteine composition for infusion to a subject to provide a therapeutically effective dose of L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof to the subject in a therapeutically effective dosing regimen.

61. The method of embodiment 57, 58, 59, or 61, wherein said administering is from 30 minutes to about 24-48 hrs.

62. The method of embodiment 61, wherein the amount of Aluminum in the composition results in a daily dosage of Aluminum from about 1 mcg/kg/day to about 4 mcg/kg/day, or about 2 mcg/kg/day to about 4 mcg/kg/day, or about 1 mcg/kg/day to about 5 mcg/kg/day, or about 2 mcg/kg/day to about 5 mcg/kg/day.

63. The method of embodiment 61 or 62, wherein the intravenous fluid is a member selected from the group consisting of: isotonic saline, glucose solution, glucose saline, dextrose solution, crystalline amino acid solution, and combinations thereof.

64. The method of embodiment 61, 62 or 63, wherein administering is performed via intravenous infusion.

65. The method of embodiment 61, 62, 63, or 64, wherein L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof is administered at a rate of from about 1 mL/min to about 10 ml/min.

66. The method of embodiment 61, 62, 63, 64 or 65, wherein the therapeutically effective dose of L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof is an amount from about 50 mg to about 1200 mg.

67. The method of embodiment 61, 62, 63, 64, 65 or 66, wherein the therapeutically effective dose of L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof is an amount of about 100-500 mg.

68. The method of embodiment 61, 62, 63, 64, 65, 66 or 67, wherein the L-cysteine is L-cysteine hydrochloride monohydrate.

69. The method of embodiment 61, 62, 63, 64, 65, 66, 67 or 68, wherein the subject is a subject in need of total parenteral nutrition (TPN).

70. The method of embodiment 61, 62, 63, 64, 65, 66, 67, 68 or 69, wherein the subject is an infant having an age of 6 months or less.

71. The method of embodiment 61, 62, 63, 64, 65, 66, 67, 68, 69, 70 or 71, wherein the therapeutically effective dosing regimen is a total parenteral nutrition (TPN) dosing regimen.

72. A method of preparing the composition of any above embodiment, comprising stirring Water for Injection, USP (WFI) in a vessel at a temperature of NMT about 60°C;

Contacting the stirring WFI with Argon until the dissolved oxygen is NMT 1 ppm;

Allowing the vessel to cool to a temperature of NMT 30°C;

Contacting under the Argon the WFI with L-Cysteine Hydrochloride, Monohydrate, USP (L-Cysteine) for NTL about 15 mins;

Continuing the mixing under Argon until the dissolved oxygen is NMT 1 ppm;

Adjusting the pH to about 1.8 with concentrated Hydrochloric Acid, NF and/or 5.0 N Sodium Hydroxide, NF;

Mixing for a minimum of about 10 minutes;

Capping the vessel under Argon and allowing to stand; and

Performing Head Space oxygen Reduction after filling, wherein the dissolved oxygen is about 0.1 ppm to about 5 ppm.

With this in mind, the following examples are intended to illustrate, but not limit, various aspects of the compositions and methods described herein.

## Examples

### Example 1

### Compounding L-Cysteine Hydrochloride Injection, USP, 50 mg/mL, 10 mL Vial

Compounding was initiated with the addition of 40 ± 1.0 kg of Water for Injection, USP (WFI) was added to the Xcellerex Mixing System via an addition funnel. A target water temperature of NMT 60°C was maintained throughout WFI addition using a heat exchanger. With continuous mixing at a speed of 126 rpm, Argon overlaying of the WFI began in the mixing bag and continued until the dissolved oxygen was NMT 1 ppm; then the mixing bag was allowed to cool to a temperature of NMT 30°C.

With continuous mixing and Argon overlaying, the L-Cysteine Hydrochloride, Monohydrate, USP (L-Cysteine) was added directly into the vortex of the mixing bag. The mixing continued for NLT 15 minutes or until complete dissolution was observed. The dissolved oxygen content was measured and recorded prior to the addition of L-Cysteine, immediately following the addition of L-Cysteine, and following the NLT 15-minute mixing period. With continuous mixing and Argon overlaying, the temperature, pH and dissolved oxygen of the solution was measured and recorded. Argon overlaying continues until the dissolved oxygen was NMT 1 ppm.

With continuous mixing and Argon overlaying, the solution's pH was adjusted to a target of 1.8 with concentrated Hydrochloric Acid, NF and/or 5.0 N Sodium Hydroxide, NF. Following pH adjustment, the solution was allowed to mix for a minimum of 10 minutes, and then the pH was verified and adjusted as needed with the Hydrochloric Acid, NF and/or N Sodium Hydroxide, NF. Then, the solution's weight, adjusted pH and dissolved oxygen was measured and recorded.

With continuous mixing and Argon overlaying, the solution was q.s.'d with the WFI to a final weight of 50.6 kg and allowed to mix for approximately 10 minutes. The

final solution weight, solution temperature, solution pH, and dissolved oxygen was then measured and recorded. Following these steps, the mixing bag was fully inflated with Argon and capped, and the solution was transferred from the mixing bag to the solution holding bag.

Example 2

L-Cysteine Injection in High Quality Glass Vials

L-Cysteine injection was compounded as per Example 1. The bulk solution was filled then using high quality glass vials (10 mL) from Schott. These vials are known as Schott Type 1 USP glass. The glass was a standard glass of pharmaceutical quality but was uncoated. The product was put on stability and was monitored for impurities, particulates, and Aluminum. The product was quite stable for all the time points tested up to 12 months. There were no unacceptable particulate counts.

However, as the data show, the product resulted in an unacceptably high aluminum content. The data for aluminum levels are shown below.

Table 6. Aluminum Levels

| Lot # | Release | 6 Months | |
|---|---|---|---|
| | | 25°C/60% RH | 40°C/75% RH |
| XMHH1609 | 212 ppb | 569 ppb | 1.306 ppb |
| XMHH1610 | 199 ppb | 748 ppb | 1,374 ppb |
| XMHH1611 | 230 ppb | 726 ppb | 1,044 ppb |

Example 3

L-Cysteine Injection in Plastic Vials

L-Cysteine injection was compounded as per Example 1. The bulk solution was filled then using plastic vials obtained from Medicopak, Inc. These vials are made of cyclic olefin copolymer (COC). The product was put on stability and was monitored for

impurities, particulates, and Aluminum. The product was not stable beyond 1 month at accelerated storage conditions and failed at room temperature conditions by the third month data point.

Table 7. Particulate levels

| **Lot Number/ Vial** | **Release** | **1 Month / 40°C/75% RH*** | **3 Month / 25°C/60% RH*** |
|---|---|---|---|
| XMHG1700/ 10 mL COC vial | Passing | Failed Visual, particulates | Failed Visual, particulates |
| XMHG1701/ 10 mL COC vial | Passing | Failed Visual, particulates | Failed Visual, particulates |
| XMHG1702/ 10 mL COC vial | Passing | Failed Visual, particulates | Failed Visual, particulates |

However, the product showed acceptable aluminum content. The data for aluminum levels are shown below.

Table 8. Aluminum Levels

| **Time Point** | **Lot XMHG 1700** | **Lot XMHG 1701** | **Lot XMHG 1702** |
|---|---|---|---|
| Time Zero | 1 ppb | 2 ppb | 1 ppb |

Aluminum at additional time points was not measured because the product was abandoned due to unacceptably high particulate count.

Example 4

Headspace Reduction and Argon Overlay

Data from Example 3 show that plastic vials do not provide the desired purity and stability of a L-cysteine composition for injection. This study was to evaluate the parameters to determine headspace oxygen reduction conditions. The product was

manufactured as per Example 1. The drug product was overlaid with Argon until the dissolved oxygen levels were no more than (NMT) 1 part per million (PPM). Vials were filled and placed in the VirTis Benchmark Lyophilizer, OP4159, for Head Space reduction. In addition, empty vials were also placed into the lyo for Head Space reduction as part of the study.

Multiple points were monitored during the manufacturing process as part of the study including the following: 1) Compounding; 2) Pre-Filling; 3) Filling; 4) Post Filling; and 5) Head Space Reduction (HSR). The monitoring involved taking dissolved oxygen (DO) measurements on drug product for filled vials throughout the manufacturing process and performing Head Space Gas Analysis on drug product for both filled and empty vials post head space reduction. Additionally, fill hold samples representing the maximum exposure during the filling step were analyzed for the dissolved oxygen and Head Space Oxygen Analysis.

The sampling and testing that was performed per the study is shown in Table 9. Samples were collected throughout the manufacturing process to determine the impact of critical process parameters on its predetermined critical quality attribute.

Table 9: Sampling and Testing Methodology

| Operation | Sample Location/Quantity | Testing Requirements | Acceptance Criteria |
|---|---|---|---|
| Compounding | The bulk solution was mixed under Argon overlaying. Measure and record final solution weight, solution temperature, solution pH, and dissolved oxygen.<br><br>Measure and record the final dissolved oxygen. | Dissolved Oxygen | Dissolved Oxygen < 1 ppm |
| Filling | For Load A [Trays 1 – 4, 17 – 20] use forceps to remove four (4) filled vials from each tray as it is filled Fully seat the stoppers of the removed filled vials immediately after removal and then label vials appropriately | Dissolved Oxygen | Dissolved Oxygen =Report Value |

| | | | |
|---|---|---|---|
| Filling Hold | As Tray 1 is loaded into the Lyo, using forceps, carefully remove 20 vials from the appropriate locations. Do not fully stopper the vials. Mark the vials "Fill Hold"<br><br>Similarly, after Tray 21 has been completely filled and is being placed into the cart, use forceps to remove twenty (20) filled vials from the appropriate<br><br>As Tray 21 is being loaded into the Lyophilizer for Head Space Reduction, use forceps to remove two (2) of the vials marked "Fill Hold", fully seat the stoppers of the vials, and label appropriately. | Dissolved Oxygen | Dissolved Oxygen =Report Value |
| Lyo Loading | For Trays 1 – 4, 17 – 20, 21 – 24, and 37 – 40, use forceps to remove two (2) filled vials, as each tray is loaded into the Lyo, fully seat the stoppers of the vials, and label appropriately | Dissolved Oxygen | Dissolved Oxygen =Report Value |
| Capping | Following headspace reduction and immediately prior to loading each tray into the RAB for capping, use forceps to remove four (4) filled vials from each tray. Place a mark on each of the removed vials for identification purposes and place the marked vials back into the tray. Load the tray into the RAB for capping. Following the capping of each tray, remove the marked vials from the tray and label appropriately. | Dissolved Oxygen<br><br>Head Space Gas Analysis | Dissolved Oxygen =Report Value<br><br>Head Space Gas Analysis =Report Value |
| Capping Fill Hold | Following headspace reduction and capping, remove the eighteen (18) vials marked "Fill Hold" from Tray 21 for testing. | Dissolved Oxygen<br><br>Head Space Gas Analysis | Dissolved Oxygen =Report Value<br><br>Head Space Gas Analysis =Report Value |

The data collected are as follows: Dissolved oxygen; Comparison of dissolved oxygen levels per tray at various stages of the manufacturing process; Filled vials head space oxygen; Held vials dissolved oxygen (ppm) and head space oxygen content (%); Comparison of Post Head Space Dissolved Oxygen (ppm) and Head Space Oxygen Content (%).

Dissolved oxygen data at various stages of the manufacturing process are shown in Table 10. A two (2) hour delay in the DO testing for the Post Filling - Pre HSR samples (Tray 1 – 4; tested using gas calibration) exhibited an average value of 11.77 ppm, an increase of 6.65 ppm from the average of 5.12 ppm measured live time after filling using the liquid calibration. Furthermore, the samples tested live time but using the gas calibration (Tray 17 – 20) exhibited an average value of 6.41 ppm, an increase of 1.29 ppm from the average of 5.12 ppm measured after filling using the liquid calibration. Starting Tray 21 of the Post Filling – Pre HSR step, the calibration was corrected to a liquid calibration. Comparison of dissolved oxygen levels at various stages of the manufacturing process is provided in Figures 1 and 2.

Table 10. Dissolved Oxygen Levels.

| Tray Number | Post Filling -Pre HSR (ppm) | Post Filling - During Loading of Lyo (ppm) | Post HSR -Capping - Filled Vials (ppm) |
|---|---|---|---|
| **1** | 11.932 | 10.179 | 0.480 |
| **2** | 11.228 | 9.925 | 0.470 |
| **3** | 11.486 | 10.577 | 0.508 |
| **4** | 12.441 | 10.370 | 0.409 |
| **17** | 6.808 | 9.893 | 0.525 |
| **18** | 6.628 | 9.859 | 0.707 |
| **19** | 5.860 | 9.854 | 0.486 |
| **20** | 6.343 | 9.720 | 0.495 |
| **21** | 5.641 | 10.329 | 0.735 |
| **22** | 5.374 | 10.308 | 0.546 |
| **23** | 5.190 | 10.149 | 0.481 |
| **24** | 7.073 | 9.844 | 0.541 |
| **37** | 4.328 | 9.544 | 0.403 |
| **38** | 3.604 | 9.251 | 0.378 |
| **39** | 4.559 | 9.265 | 0.390 |
| **40** | 5.173 | 9.577 | 0.369 |

| | | | |
|---|---|---|---|
| **Average** | **5.117** | **9.915** | **0.495** |
| **STD** | 1.03 | 0.39 | 0.11 |
| **%RSD** | **20.1** | **3.9** | **21.3** |

Table 11. Filled Vials Head Space Oxygen.

| Tray Number | Post HSR -Capping - Filled Vials (% Oxygen) | Post Capping - Empty Vials (% Oxygen) |
|---|---|---|
| **1** | 1.147 | 0.981 |
| **2** | 1.399 | 1.116 |
| **3** | 1.551 | 0.980 |
| **4** | 0.950 | 1.139 |
| **17** | 1.382 | 1.156 |
| **18** | 1.766 | 1.236 |
| **19** | 1.154 | 1.224 |
| **20** | 1.265 | 1.180 |
| **21** | 1.844 | 1.221 |
| **22** | 1.365 | 1.169 |
| **23** | 0.890 | 1.295 |
| **24** | 1.148 | 1.114 |
| **37** | 0.880 | 1.300 |
| **38** | 0.871 | 1.151 |
| **39** | 0.850 | 1.097 |
| **40** | 0.889 | 1.042 |
| **Average** | **1.209** | **1.150** |
| **STD** | 0.32 | 0.10 |
| **%RSD** | **26.7** | **8.3** |

Table 12. Held vials dissolved oxygen (ppm) and head space oxygen content (%).

| Held Vials– Tray 1 / Tray 21 | Dissolved Oxygen Post Filling – Loading of Lyo (ppm) | Dissolved Oxygen Post HSR – Capping – Filled Vials (ppm) | Head Space Oxygen % Post HSR- Capping – Filled Vials (%) |
|---|---|---|---|
| **Sample 1** | 10.685 | 0.578 | 1.563 |
| **Sample 2** | 10.467 | 0.588 | 1.390 |
| **Sample 3** | - | 0.565 | 1.522 |
| **Sample 4** | - | 0.550 | 1.447 |
| **Average** | **10.576** | **0.570** | **1.481** |
| **STD** | 0.15 | 0.02 | 0.08 |
| **%RSD** | **1.5** | **2.9** | **5.2** |

Table 13. Comparison of Post Head Space Dissolved Oxygen (ppm) and Head Space Oxygen Content (%).

| | Dissolved Oxygen Pre HSR (ppm) | Dissolved Oxygen Post HSR – (ppm) | Head Space Oxygen % Post HSR (%) |
|---|---|---|---|
| PROT-000055 Study Empty Vials Avg. | - | - | 1.150 |
| PROT-000055 Study Filled Vials Avg. | 9.915 | 0.495 | 1.209 |
| 2018-RD-022 Study Empty Vials Avg. | - | - | 0.49 |
| 2018-RD-022 Study Filled Vials Avg. | 7.14 | 2.55 | 1.27 |
| Lot XMHJ1705 | - | 0.637 | 2.28 |
| Lot XMHJ1706 | - | 0.391 | 1.92 |
| Lot XMHJ1707 | - | 1.585 | 1.94 |

The results from these experiments demonstrate the effectiveness of the Head Space Reduction (HSR) cycle in attaining reduced and consistent dissolved oxygen (DO) levels in the finished drug product. The results showed a trend with an increase in dissolved oxygen level from 0.36 parts per million (ppm) recorded during compounding, to an average of 5.12 ppm measured after filling, a further increase to an average of 9.92 ppm while loading the Lyophilizer, and finally a reduction of dissolved oxygen to an average of 0.50 ppm after headspace reduction. The overall trends are displayed in Figures 1 and 2. The plots and data also show that the average increase in dissolved oxygen levels from compounding to the filled vials was 4.76 ppm. Also, as the vials were stored in the transfer cart, an average dissolved oxygen increase of about 4.80 ppm was observed prior to being loaded in the Lyophilizer for head space reduction. The total average increase in dissolved oxygen levels from compounding to vials being loaded in the lyophilizer was 9.56 ppm. The average decrease in dissolved oxygen observed in vials post head space reduction was 9.42 ppm. In addition, the oxygen levels obtained across all trays analyzed pre and post HSR were consistent throughout the manufacturing process.

Head Space Gas Analysis was performed on both filled and empty vials taken from designated locations in selected trays. Percent (%) Oxygen results achieved across the trays showed a relatively uniform head space reduction process throughout the chamber. The average % Oxygen for the empty vials was found to be 1.15%, compared with 1.21% for the filled vials (Reference Table 11).

Dissolved Oxygen and Head Space Gas Analysis were also performed on the Held Vials from designated locations in Tray 1 as part of the stressed sample analysis over the course of the manufacturing process. The results showed a comparable trend to that observed for the regular samples across the study (Reference Table 12). Specifically, an increase in dissolved oxygen level from 0.36 ppm recorded during compounding, to 5.64 ppm measured after filling, a further increase to an average of 10.58 ppm while loading the Lyophilizer, and finally a reduction of dissolved oxygen to an average of 0.57 ppm after headspace reduction. The average % Oxygen for the filled held vials was found to be 1.48%, compared with 1.21% for the filled regular vials. This indicated that the HSR cycle was effective in achieving comparable DO and Headspace oxygen results irrespective of the maximum fill time exposure (approximately 7 hours; represented by the Fill Hold Vials) and has no impact on the quality of the product. The use of the Lyophilizer, in the Head Space Reduction of L-Cysteine Hydrochloride Injection, USP (50 mg/mL) has been shown to be effective for the control of reduced and consistent oxygen levels, and is suitable for scale up for the existing process and equipment as the product meets all the critical quality attributes.

Example 5

Head space oxygen reduction was accomplished using an automated filling equipment that can handle high speed filling, in contrast to slow or low volume operation such as through a lyophilizer as described in Examples 1 and 4. The high-speed filler is capable of using vacuum and gas overlay in alternate pulses to reduce the head space oxygen. Each pulse is timed to be within 0.1 to 5 seconds such that typically 3-5 pulses are conducted in one head space oxygen reduction cycle. The pulse rate can be adjusted after

multiple trials to provide optimal headspace reduction with optimal speed of the filler such that no product is lost through back suction or through spillage and average speeds of from about 20 vials/minute to about 200 vials per minute, depending on the number of fill heads used.

A 50 L batch was prepared utilizing the current compounding procedure described above in Example 1. The filler was set up to fill and reduce head space oxygen as per the process shown in Figure 3.

The total head space reduction cycle lasted about 25 seconds per operation. The vials were analyzed for head space oxygen at time zero and at 1-month time point. The data are shown below.

The evaluation of the filler's performance demonstrated that the headspace oxygen control was comparable to or better than the current process for L-Cysteine. Headspace oxygen values obtained ranged from 0.2% to 0.5% for all vials filled, including empty vials during start up. Vials tested after 1-month storage at ambient conditions also maintain headspace oxygen levels between 0.4 and 1.5%. The Tables below show a summary of the results for the in process and 1-month stability testing. Also included below is a comparison of the in-process data obtained from previously manufactured lots of L-Cysteine utilizing the lyophilizer headspace reduction method. The data show the headspace oxygen values at Time Zero are lower with the high-speed filler than the lyophilizer process.

Table 14. Headspace Oxygen Levels at Time Zero for High-Speed Filler

| PROT-000213 – Time Zero | | | | | |
|---|---|---|---|---|---|
| | Tray 5 | Tray 10 | Overall Low | Overall High | Average |
| Headspace $O_2$ (%) | 0.473 | 0.378 | 0.243 | 0.490 | 0.372 |

Table 15. Headspace Oxygen Levels at 1 Month for High-Speed Filler

| PROT-000213 – 1 Month | | |
|---|---|---|
| | Tray No. 5 | Tray No. 10 |

| | Low | High | Average | Low | High | Average |
|---|---|---|---|---|---|---|
| **Headspace $O_2$ (%)** | 0.412 | 1.518 | 0.995 | 0.98 | 1.454 | 1.262 |

Table 16. Comparison of Headspace Oxygen Levels between Lyophilizer and High-Speed Filler Operations

| **Batch (Process)** | **XMHJ1705 (Current Process)** | **XMHJ1706 (Current Process)** | **XMHJ1707 (Current Process)** | **PROT-000213 (High Speed Filler)** |
|---|---|---|---|---|
| Average<br>Low<br>High | 2.3 % Oxygen<br>N/A<br>N/A | 1.9 % Oxygen<br>N/A<br>N/A | 1.9 % Oxygen<br>N/A<br>N/A | 0.4 % Oxygen<br>0.2% Oxygen<br>0.5% Oxygen |
| 1 Month Room Temperature | 0.9 % Oxygen | 2.8 % Oxygen | 1.2 % Oxygen | 1.1 % Oxygen<br>(0.4 % to 1.5 %) |

N/A – Not Applicable

Figure 4 shows the comparison of oxygen headspace control between the lyophilizer chamber headspace control method versus the high-speed filler vacuum stoppering system. The lyophilizer chamber for headspace reduction was utilized for lots XMHJ1705, XMHJ1706, and XMHJ1707 of L-Cysteine Hydrochloride injection. The time zero oxygen headspace results for the engineering batch PROT-000213 are shown in comparison to the previously manufactured lots. Results shown were measured at the time of manufacturing on samples of vials from the batches. Oxygen percentage was taken for the samples from PROT-000213 using the NeoFox Phase Fluorometer. Lots XMHJ1705, XMHJ1706, and XMHJ1707 used Argon Headspace Analysis, QCTM-000014.

In addition to the head space oxygen levels, dissolved oxygen levels were also measured. Data are shown in Figure 5.

The dissolved oxygen levels and head space oxygen levels were measured again at 1 month stability time point at room temperature conditions:

Table 17. Headspace and Dissolved Oxygen Data Comparison at 1 month

| **Study – 1 Month** |
|---|

| | Tray No. 5 | | | | Tray No. 10 | | |
|---|---|---|---|---|---|---|---|
| | Sample 1 | Sample 2 | Sample 3 | Sample 4 | Sample 1 | Sample 2 | Sample 3 |
| Headspace $O_2$ (%) | 0.576 | 0.412 | 1.518 | 1.475 | 0.98 | 1.454 | 1.352 |
| Dissolved $O_2$ (ppm) | 0.545 | 0.706 | 2.328 | 2.042 | 2.173 | 2.372 | 2.149 |

Example 6

Purity Profile and Long-Term Stability of L-Cysteine Composition for Injection

An L-cysteine composition for injection was manufactured as described in Example 1. The glass used was Schott Type 1 USP Plus glass, internally coated with silicon dioxide. The composition was subjected to stability testing to evaluate the stability of the composition over time. Table 18 shows various stability data collected for the L-cysteine composition for injection over a 9-month testing period. Samples of exhibit batches stored upright at room temperature for 9 months at 25 °C/ 60% RH. Note: two samples were tested for dissolved oxygen and head-space oxygen.

Table 18. Characterization of L-Cysteine Composition for Injection

| Test | XMHJ1705 | XMHJ1706 | XMHJ1707 |
|---|---|---|---|
| | Up | Up | Up |
| L-Cysteine HCl | 100.4% | 101.3% | 101.2% |
| Related Compounds:<br>L-Cystine<br>Pyruvic Acid Total<br>Specified RRT-1.98<br>Individual<br>Unspecified<br>Total Impurities | <br>0.3%<br>0.1%<br>0.2%<br>ND<br>0.5% | <br>0.3%<br>0.2%<br>0.2%<br>ND<br>0.7% | <br>0.3%<br>0.1%<br>0.2%<br>ND<br>0.6% |
| Dissolved Oxygen | (1) 0.12 ppm<br>(2) 0.13 ppm | (1) 0.13 ppm<br>(2) 0.14 ppm | (1) 0.14 ppm<br>(2) 0.13 ppm |
| Head-Space Oxygen | (1) 0.16%<br>(2) 0.37% | (1) 0.53%<br>(2) 0.89% | (1) 0.56%<br>(2) 0.50% |
| Aluminum Content | 3.2 ppb | 2.9 ppb | 5.6 ppb |
| Description | Clear colorless solution | Clear colorless solution | Clear colorless solution |

Example 7

Effect of Dissolved Oxygen and Headspace Oxygen on L-cysteine and Cystine Levels

An L-cysteine composition for injection was manufactured as described in Example 1. However, samples of exhibit batches were tested without head-space reduction and argon overlay during compounding, then filled, stoppered and capped. Samples were tested within one week of manufacturing date. Data in Table 19 show the marked effects of lack of headspace and dissolved oxygen on component levels within one week. L-Cystine increased by about 0.4% - 0.7% within a week for samples with higher dissolved oxygen and head-space oxygen.

Table 19. Effect of lack of Headspace and Dissolved Oxygen Control on Product Purity

| **Test** | **Prior to Head-Space Reduction Tray 1** | **Prior to Head-Space Reduction Tray 19** | **Prior to Head-Space Reduction Tray 23** | **Ave Values for after completed Batch** |
|---|---|---|---|---|
| L-Cysteine HCl | 99.9% | 100.1% | 100.0% | 102.0% |
| L-Cystine | 0.8% | 0.5% | 0.6% | 0.1% |
| Head-Space Oxygen | 20.8% | 20.3% | 20.3% | 1.2% |
| Dissolved Oxygen | 8.3 ppm | 8.6 ppm | 8.6 ppm | 0.50 ppm |

Example 8

Evaluation of Anions in L-Cysteine Product

Inorganic anionic leachables were determined using validated potentiometric methods utilizing ion selective electrodes. Fluoride and Iodide were evaluated for this drug product. The leachables testing results are listed in Tables 20 and 21 below.

Table 20. Leachable Iodide Results for L-Cysteine HCl Injection
[$I^-$] (ppb)

| | XMHJ1705 | | | | | |
|---|---|---|---|---|---|---|
| | 25°C/60% RH | | | 40°C/75% RH | | |
| Replicate | Upright | Horizontal | Inverted | Upright | Horizontal | Inverted |
| 1 | 28.1 | 27.4 | 27.1 | 25.2 | 24.9 | 24.7 |
| 2 | 25.9 | 26.3 | 25.9 | 24.0 | 24.1 | 24.1 |
| 3 | 28.1 | 25.3 | 25.3 | 24.0 | 22.3 | 21.6 |
| Average | 27.4 | 26.3 | 26.1 | 24.4 | 23.7 | 23.5 |
| SD | 1.3 | 1.0 | 0.9 | 0.7 | 1.3 | 1.6 |
| % RSD | 4.7 | 3.9 | 3.6 | 2.7 | 5.6 | 7.0 |
| | XMHJ1706 | | | | | |
| | 25°C/60% RH | | | 40°C/75% RH | | |
| Replicate | Upright | Horizontal | Inverted | Upright | Horizontal | Inverted |
| 1 | 81.7 | 80.3 | 82.8 | 80.3 | 82.0 | 81.8 |
| 2 | 83.1 | 81.7 | 81.5 | 82.5 | 82.3 | 81.3 |
| 3 | 81.7 | 81.7 | 81.8 | 78.1 | 81.9 | 82.8 |
| Average | 82.2 | 81.2 | 82.0 | 80.3 | 82.1 | 82.0 |
| SD | 0.8 | 0.8 | 0.7 | 2.2 | 0.2 | 0.7 |
| % RSD | 0.9 | 1.0 | 0.9 | 2.7 | 0.2 | 0.9 |
| | XMHJ1707 | | | | | |
| | 25°C/60% RH | | | 40°C/75% RH | | |
| Replicate | Upright | Horizontal | Inverted | Upright | Horizontal | Inverted |
| 1 | 53.5 | 52.3 | 53.1 | 51.7 | 51.4 | 50.8 |
| 2 | 52.5 | 54.0 | 53.7 | 51.8 | 52.0 | 53.5 |
| 3 | 54.4 | 52.8 | 52.8 | 53.8 | 53.6 | 52.6 |
| Average | 53.5 | 53.0 | 53.2 | 52.4 | 52.3 | 52.3 |
| SD | 1.0 | 0.9 | 0.4 | 1.2 | 1.1 | 1.4 |
| % RSD | 1.8 | 1.7 | 0.8 | 2.2 | 2.1 | 2.6 |

.

Table 21. Leachable Iodide Results for L-Cysteine HCl Injection
[$I^-$] (ppb)

| | XMHL1702A | | XMHL1702B | |
|---|---|---|---|---|
| | 25 °C/60 %RH 6 month | 40 °C/75 %RH 6 month | 25 °C/60 %RH 6 month | 40 °C/75 %RH 6 month |
| Iodide (ppb) | 29 | 24 | 24 | 19 |

The leachable results for Fluoride indicate levels below 20 ppb and no observable trend in leachable amount over time or temperature dependence. The leachable results for Iodide indicate that levels were observed ranging from ~20-80 ppb. No noticeable trend in leachable amount including vial orientation or temperature dependence was observed.

Example 9

Elemental Leachables

Elemental leachables were evaluated using a validated inductively coupled plasma mass spectrometric (ICP-MS) method. ICP-MS method is described in detail in USP and other literature in the art. The results for the elemental leachables analysis are summarized in the Table below. The Table lists the Allowable Elemental Concentrations (AEC) for each identified element.

Table 22. Elemental Impurity Leachables Results for L-Cysteine HCl Injection [X] (ppb)

| **Element** | **AEC (ppb)** | **XMHJ1705 25 $^{O}$C/60 %RH** | | | | **XMHJ1705 40 $^{O}$C/75 %RH** | | |
|---|---|---|---|---|---|---|---|---|
| | | **Time point (months)** | | | | | | |
| | | **1** | **3** | **6** | **9** | **1** | **3** | **6** |
| Molybdenum | 14537 | <0.5 | 2 | 1.75 | 0.6 | <0.5 | 2 | 0.91 |
| Zinc | 12598 | 14 | 2 | 13.84 | 23.4 | 11 | 38 | <QL |
| Iron | 12598 | 25 | 21 | 50.52 | 19 | 16 | 60 | 5.73 |
| Chromium | 10660 | 2 | <QL | <QL | 3.2 | 2 | 6 | <QL |
| Barium | 6784 | 2 | <QL | <QL | <QL | <0.5 | 2 | <QL |
| Tin | 5815 | 1 | 2 | 3.38 | 1.2 | | 3 | 0.88 |
| Copper | 2907 | <0.5 | <QL | <QL | 15.0 | <0.5 | 2 | <QL |
| Manganese | 2423 | 1 | <QL | <QL | 0.3 | <0.5 | 2 | <QL |
| Lithium | 2423 | <0.5 | 5 | 3.90 | 0.1 | <0.5 | 6 | 3.79 |
| Gold | 969 | 5 | 3 | 9.76 | 0.3 | 3 | 4 | 1.76 |
| Antimony | 872 | 1 | 1 | 0.88 | 0.1 | 1 | 2 | 0.60 |
| Selenium | 775 | <0.5 | <QL | <QL | 0.1 | <0.5 | 2 | <QL |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Nickel | 194 | 11 | 9 | 16.66 | 8.1 | 11 | 9 | 0.99 |
| Arsenic | 174 | 1 | <QL | <QL | 0.2 | 1 | 2 | <QL |
| Aluminum | 120 | <QL | <QL | <QL | <QL | <QL | <QL | <QL |
| Vanadium | 97 | <QL | <QL | <QL | <QL | <0.5 | 4 | <QL |
| Silver | 97 | <0.5 | <QL | <QL | <QL | <QL | 17 | <QL |
| Ruthenium | 97 | <0.5 | 1 | 0.72 | <QL | <0.5 | 2 | 0.74 |
| Rhodium | 97 | <0.5 | 4 | 4.31 | <QL | <0.5 | 8 | 4.29 |
| Platinum | 97 | <0.5 | <0.5 | <QL | <QL | <0.5 | 1 | <QL |
| Palladium | 97 | <0.5 | <QL | <QL | <QL | <0.5 | 1 | <QL |
| Osmium | 97 | <0.5 | <QL | <QL | <QL | <0.5 | 1 | <QL |
| Iridium | 97 | <0.5 | 6 | 5.98 | <QL | <0.5 | 7 | 5.92 |
| Thallium | 78 | <0.5 | 4 | 3.59 | <QL | <0.5 | 5 | 3.59 |
| Cobalt | 48 | <0.5 | <QL | <QL | 0.1 | <0.5 | <0.5 | <QL |
| Lead | 48 | 2 | 5 | 6.77 | 1.5 | 2 | 6 | 3.33 |
| Mercury | 29 | <0.5 | 1 | 0.78 | 2 | <0.5 | 1 | 1.10 |
| Cadmium | 19 | <0.5 | 1 | 1.31 | <QL | <0.5 | 2 | 1.30 |

Table 22. (cont.) Elemental Impurity Leachables Results for L-Cysteine HCl Injection [X] (ppb)

| Element | AEC (ppb) | XMHJ1705 25 $^{O}$C/60 %RH | | |
|---|---|---|---|---|
| | | Time point (months) | | |
| | | 12 INV | 12 HOR | 12 UP |
| Molybdenum | 14537 | 0.4 | 0.4 | 0.5 |
| Zinc | 12598 | 7 | 5 | 3 |
| Iron | 12598 | 9 | 157 | 637 |
| Chromium | 10660 | 1 | 2 | 3 |
| Barium | 6784 | 0.4 | 0.4 | 0.4 |
| Tin | 5815 | 1 | 1 | 1 |
| Copper | 2907 | 0.5 | 0.8 | 0.6 |
| Manganese | 2423 | <QL | 2 | 8 |
| Lithium | 2423 | 0.04 | 0.05 | 0.05 |
| Gold | 969 | 0.4 | <QL | 1 |
| Antimony | 872 | 0.4 | 0.3 | 0.3 |
| Selenium | 775 | <QL | 1 | <QL |
| Nickel | 194 | 14 | 14 | 15 |
| Arsenic | 174 | 0.3 | 0.3 | 0.2 |
| Aluminum | 120 | (4) <QL | (19) <QL | (5) <QL |
| Vanadium | 97 | <QL | <QL | <QL |
| Silver | 97 | <QL | <QL | <QL |
| Ruthenium | 97 | <QL | <QL | <QL |
| Rhodium | 97 | 0.01 | 0.01 | 0.01 |
| Platinum | 97 | <QL | <QL | <QL |
| Palladium | 97 | 0.06 | 0.06 | 0.1 |
| Osmium | 97 | <QL | <QL | <QL |
| Iridium | 97 | 0.04 | 0.03 | 0.04 |
| Thallium | 78 | <QL | <QL | <QL |
| Cobalt | 48 | <QL | <QL | <QL |
| Lead | 48 | 2 | 2 | 2 |
| Mercury | 29 | 0.7 | 0.7 | 0.6 |
| Cadmium | 19 | <QL | <QL | <QL |

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Table 22. (cont.) Elemental Impurity Leachables Results for L-Cysteine HCl Injection [X] (ppb)

| Element | AEC (ppb) | XMHJ1706 25 °C/60 %RH | | | | XMHJ1706 40 °C/75 %RH | | |
|---|---|---|---|---|---|---|---|---|
| | | Time point (months) | | | | | | |
| | | 1 | 3 | 6 | 9 | 1 | 3 | 6 |
| Molybdenum | 14537 | <0.5 | 1 | 1.32 | 0.4 | <0.5 | 2 | 1.33 |
| Zinc | 12598 | 10 | 8 | 8.23 | 23.9 | 10 | 36 | 4.25 |
| Iron | 12598 | 9 | 30 | 34.02 | 7.9 | 10 | 41 | 45.60 |
| Chromium | 10660 | 1 | <QL | <QL | 1.9 | 2 | 5 | <QL |
| Barium | 6784 | <0.5 | <QL | <QL | <QL | 1 | 1 | <QL |
| Tin | 5815 | 1 | 2 | 2.91 | 1.3 | 1 | 3 | 2.08 |
| Copper | 2907 | <QL | <QL | <QL | <QL | <QL | 1 | <QL |
| Manganese | 2423 | <0.5 | <QL | <QL | 0.3 | <0.5 | 1 | <QL |
| Lithium | 2423 | <0.5 | 4 | 3.84 | 0.1 | <0.5 | 6 | 3.87 |
| Gold | 969 | 2 | 3 | 4.38 | 0.2 | 2 | 4 | 3.99 |
| Antimony | 872 | 1 | 1 | 0.81 | <QL | 1 | 2 | 0.91 |
| Selenium | 775 | <0.5 | <QL | <QL | 0.6 | 1 | 3 | <QL |
| Nickel | 194 | 11 | 10 | 8.66 | 8.1 | 11 | 9 | 8.68 |
| Arsenic | 174 | <0.5 | <QL | <QL | 0.4 | <0.5 | 2 | <QL |
| Aluminum | 120 | <QL | <QL (2) | <QL | <QL | <QL | <QL | <QL |
| Vanadium | 97 | <QL | <QL | <QL | <QL | <0.5 | 4 | <QL |
| Silver | 97 | <QL | <QL | <QL | <QL | <QL | 17 | <QL |
| Ruthenium | 97 | <0.5 | 1 | 0.73 | <QL | <0.5 | 2 | 0.73 |
| Rhodium | 97 | <0.5 | 4 | 4.29 | <QL | <0.5 | 8 | 4.28 |
| Platinum | 97 | <0.5 | <0.5 | <QL | <QL | <0.5 | 1 | <QL |
| Palladium | 97 | <0.5 | <QL | <QL | <QL | <0.5 | 1 | <QL |
| Osmium | 97 | <0.5 | <QL | <QL | <QL | <0.5 | 1 | <QL |
| Iridium | 97 | <0.5 | 6 | 5.94 | <QL | <0.5 | 7 | 5.94 |
| Thallium | 78 | <0.5 | 4 | 3.59 | <QL | <0.5 | 5 | 3.59 |
| Cobalt | 48 | <0.5 | <0.5 | <QL | <QL | <0.5 | <0.5 | <QL |
| Lead | 48 | 2 | 6 | 5.53 | 2.0 | 2 | 6 | 5.53 |
| Mercury | 29 | <0.5 | 1 | 1.11 | 1.5 | <0.5 | 1 | 1.01 |
| Cadmium | 19 | <0.5 | 1 | 1.30 | <QL | <0.5 | 2 | 1.30 |

Table 22. (cont.) Elemental Impurity Leachables Results for L-Cysteine HCl Injection [X] (ppb)

| Element | AEC (ppb) | XMHJ1706 25 $^{O}$C/60 %RH | | |
|---|---|---|---|---|
| | | Time point (months) | | |
| | | 12 INV | 12 HOR | 12 UP |
| Molybdenum | 14537 | 0.4 | 0.4 | 0.4 |
| Zinc | 12598 | 3 | 6 | 8 |
| Iron | 12598 | 11 | 55 | 10 |
| Chromium | 10660 | 1 | 1 | 1 |
| Barium | 6784 | 0.4 | 0.6 | 0.4 |
| Tin | 5815 | 1 | 2 | 2 |
| Copper | 2907 | 1 | 0.2 | <QL |
| Manganese | 2423 | 0.1 | 0.6 | 0.2 |
| Lithium | 2423 | 0.03 | 0.03 | 0.04 |
| Gold | 969 | 0.2 | 0.2 | 0.3 |
| Antimony | 872 | 0.6 | 0.5 | 0.5 |
| Selenium | 775 | 0.4 | <QL | 0.4 |
| Nickel | 194 | 14 | 14 | 14 |
| Arsenic | 174 | 0.8 | 0.5 | 0.4 |
| Aluminum | 120 | (5) <QL | (6) <QL | (1) <QL |
| Vanadium | 97 | <QL | <QL | <QL |
| Silver | 97 | <QL | <QL | <QL |
| Ruthenium | 97 | 0.005 | <QL | 0.003 |
| Rhodium | 97 | 0.007 | 0.005 | 0.008 |
| Platinum | 97 | <QL | <QL | <QL |
| Palladium | 97 | 0.04 | 0.02 | 0.03 |
| Osmium | 97 | <QL | <QL | <QL |
| Iridium | 97 | 0.03 | 0.03 | 0.03 |
| Thallium | 78 | <QL | <QL | <QL |
| Cobalt | 48 | <QL | <QL | <QL |
| Lead | 48 | 2 | 2 | 2 |
| Mercury | 29 | 0.7 | 0.7 | 0.7 |
| Cadmium | 19 | <QL | 0.004 | <QL |

Table 22. (cont.) Elemental Impurity Leachables Results for L-Cysteine HCl Injection [X] (ppb)

| Element | AEC (ppb) | XMHJ1707 25 °C/60 %RH | | | | XMHJ1707 40 °C/75 %RH | | |
|---|---|---|---|---|---|---|---|---|
| | | Time point (months) | | | | | | |
| | | 1 | 3 | 6 | 9 | 1 | 3 | 6 |
| Molybdenum | 14537 | <0.5 | 1 | 1.22 | 0.4 | <0.5 | 2 | 1.21 |
| Zinc | 12598 | 10 | 4 | 4.28 | 22.7 | 11 | 38 | 3.91 |
| Iron | 12598 | 8 | 26 | 12.55 | 8.3 | 9 | 74 | 17.68 |
| Chromium | 10660 | 1 | <QL | <QL | 2.2 | 1 | 6 | <QL |
| Barium | 6784 | <0.5 | <0.5 | <QL | <QL | <0.5 | 1 | <QL |
| Tin | 5815 | 1 | 2 | 2.13 | 3.2 | 1 | 3 | 2.22 |
| Copper | 2907 | <0.5 | <QL | <QL | <QL | <0.5 | 2 | <QL |
| Manganese | 2423 | <0.5 | <QL | <QL | 0.1 | <0.5 | 1 | <QL |
| Lithium | 2423 | <0.5 | 3.86 | 3.86 | 0.2 | <0.5 | 6 | 3.88 |
| Gold | 969 | 3 | 3 | 3.98 | 0.1 | 2 | 4 | 3.48 |
| Antimony | 872 | 1 | 1 | 1.01 | <QL | 1 | 2 | 1.06 |
| Selenium | 775 | <0.5 | <QL | <QL | 0.1 | <0.5 | 2 | <QL |
| Nickel | 194 | 11 | 8 | 7.71 | 7.4 | 10 | 8 | 7.82 |
| Arsenic | 174 | 1 | <QL | <QL | 0.4 | 1 | 2 | <QL |
| Aluminum | 120 | <QL | <QL | <QL | <QL | <QL | <QL | <QL |
| Vanadium | 97 | <QL | <QL | <QL | <QL | <0.5 | 4 | <QL |
| Silver | 97 | <0.5 | <QL | <QL | <QL | <QL | 17 | <QL |
| Ruthenium | 97 | <0.5 | 1 | 0.73 | <QL | <0.5 | 2 | 0.73 |
| Rhodium | 97 | <0.5 | 4 | 4.29 | <QL | <0.5 | 8 | 4.28 |
| Platinum | 97 | <0.5 | <0.5 | <QL | <QL | <0.5 | 1 | <QL |
| Palladium | 97 | <0.5 | <QL | <QL | <QL | <0.5 | 1 | <QL |
| Osmium | 97 | <0.5 | <QL | <QL | <QL | <0.5 | 1 | <QL |
| Iridium | 97 | <0.5 | 6 | 5.95 | <QL | <0.5 | 7 | 5.94 |
| Thallium | 78 | <0.5 | 4 | 3.59 | <QL | <0.5 | 5 | 3.56 |
| Cobalt | 48 | <0.5 | <0.5 | <QL | <QL | <0.5 | <0.5 | <QL |
| Lead | 48 | 2 | 6 | 5.51 | 1.9 | 2 | 6 | 5.55 |
| Mercury | 29 | <0.5 | 1 | 0.98 | 1.2 | <0.5 | 1 | 0.89 |
| Cadmium | 19 | <0.5 | 1.30 | 1.29 | <QL | <0.5 | 2 | 1.29 |

Table 22. (cont.) Elemental Impurity Leachables Results for L-Cysteine HCl Injection [X] (ppb)

| Element | AEC (ppb) | XMHJ1707 25 $^{O}$C/60 %RH | | |
|---|---|---|---|---|
| | | Time point (months) | | |
| | | 12 INV | 12 HOR | 12 UP |
| Molybdenum | 14537 | 0.4 | 0.4 | 0.4 |
| Zinc | 12598 | 7 | 4 | 6 |
| Iron | 12598 | 8 | 71 | 13 |
| Chromium | 10660 | 1 | 1 | 1 |
| Barium | 6784 | 0.6 | 0.5 | 0.6 |
| Tin | 5815 | 1 | 1 | 1 |
| Copper | 2907 | 0.2 | 0.2 | 0.1 |
| Manganese | 2423 | 0.2 | 1 | 0.3 |
| Lithium | 2423 | 0.03 | 0.03 | 0.06 |
| Gold | 969 | 0.1 | 0.1 | 0.2 |
| Antimony | 872 | 0.6 | 0.6 | 0.6 |
| Selenium | 775 | 0.4 | <QL | <QL |
| Nickel | 194 | 14 | 14 | 14 |
| Arsenic | 174 | 0.6 | 0.6 | 0.6 |
| Aluminum | 120 | (5) <QL | (26) <QL | (39) <QL |
| Vanadium | 97 | <QL | <QL | <QL |
| Silver | 97 | <QL | <QL | <QL |
| Ruthenium | 97 | <QL | 0.004 | 0.001 |
| Rhodium | 97 | 0.005 | 0.005 | 0.006 |
| Platinum | 97 | <QL | <QL | <QL |
| Palladium | 97 | <QL | 0.02 | 0.02 |
| Osmium | 97 | <QL | <QL | <QL |
| Iridium | 97 | 0.03 | 0.03 | 0.03 |
| Thallium | 78 | <QL | <QL | <QL |
| Cobalt | 48 | <QL | <QL | <QL |
| Lead | 48 | 2 | 2 | 2 |
| Mercury | 29 | 0.7 | 0.7 | 0.7 |
| Cadmium | 19 | <QL | <QL | <QL |

Table 22. (cont.) Elemental Impurity Leachables Results for L-Cysteine HCl Injection [X] (ppb)

| Element | AEC (ppb) | XMHJ1702A 25 °C/60 %RH | |
|---|---|---|---|
| | | Time point (months) | |
| | | 9 INV | 9 UP |
| Molybdenum | 14537 | 1 | 0.5 |
| Zinc | 12598 | 17 | 17 |
| Iron | 12598 | 5 | 59 |
| Chromium | 10660 | 5 | 1 |
| Barium | 6784 | 1 | 0.4 |
| Tin | 5815 | 2 | 1 |
| Copper | 2907 | 1 | 0.4 |
| Manganese | 2423 | 2 | 1 |
| Lithium | 2423 | 8 | 0.1 |
| Gold | 969 | 7 | 1 |
| Antimony | 872 | <QL | 0.3 |
| Selenium | 775 | <QL | <QL |
| Nickel | 194 | 11 | 15 |
| Arsenic | 174 | 0.3 | 0.1 |
| Aluminum | 120 | (9) <QL | (5) <QL |
| Vanadium | 97 | 3 | <QL |
| Silver | 97 | 2 | <QL |
| Ruthenium | 97 | 0.9 | <QL |
| Rhodium | 97 | 8 | 0.01 |
| Platinum | 97 | 2 | <QL |
| Palladium | 97 | 1 | 0.1 |
| Osmium | 97 | 0.8 | <QL |
| Iridium | 97 | 10 | 0.04 |
| Thallium | 78 | 7 | <QL |
| Cobalt | 48 | 3 | 0.03 |
| Lead | 48 | 8 | 2 |
| Mercury | 29 | 1 | 0.6 |
| Cadmium | 19 | 0.5 | <QL |

Table 22. (cont.) Elemental Impurity Leachables Results for L-Cysteine HCl Injection [X] (ppb)

| Element | AEC (ppb) | XMHJ1702A 25 °C/60 %RH | | | | | XMHJ1702A 40 °C/75 %RH | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Time point (months) | | | | | | | | | |
| | | 0 | 1 | 2 | 3 | 6 | 0 | 1 | 2 | 3 | 6 |
| Molybdenum | 14537 | 2 | N/A | N/A | 1.34 | 0.5 | 2 | 2 | <0.5 | 1 | 0.4 |
| Zinc | 12598 | 42 | N/A | N/A | 3.90 | 34.3 | 42 | 37 | 2 | 4 | 22.1 |
| Iron | 12598 | 284 | N/A | N/A | 15.31 | 7 | 284 | 27 | <QL | 35 | 11.2 |
| Chromium | 10660 | 14 | N/A | N/A | <QL | 2.1 | 14 | 4 | <0.5 | <QL | 2.1 |
| Barium | 6784 | 2 | N/A | N/A | <QL | <QL | 2 | 2 | <QL | <QL | <QL |
| Tin | 5815 | 3 | N/A | N/A | 1.82 | 3.8 | 3 | 3 | 2 | 2 | 1 |
| Copper | 2907 | 4 | N/A | N/A | <QL | 123.1 | 4 | 2 | <QL | <QL | 0.1 |
| Manganese | 2423 | 5 | N/A | N/A | <QL | 0.1 | 5 | 1 | <0.5 | <QL | 0.3 |
| Lithium | 2423 | 6 | N/A | N/A | 3.92 | 0.2 | 6 | 6 | <QL | 4 | 0.2 |
| Gold | 969 | 7 | N/A | N/A | 3.45 | 0.1 | 7 | 4 | 5 | 4 | 0.1 |
| Antimony | 872 | 2 | N/A | N/A | 1.08 | <QL | 2 | 2 | 1 | 1 | <QL |
| Selenium | 775 | 4 | N/A | N/A | <QL | 0.4 | 4 | 2 | <QL | <QL | <QL |
| Nickel | 194 | 11 | N/A | N/A | 8.93 | 8 | 11 | 9 | 4 | 8 | 8.1 |
| Arsenic | 174 | 2 | N/A | N/A | <QL | 0.3 | 2 | 1 | <QL | <QL | 0.3 |
| Aluminum | 120 | <0.5 | N/A | N/A | <QL | <QL | <QL | (3) <QL | (8) <QL | (7) <QL | <QL |
| Vanadium | 97 | 4 | N/A | N/A | <QL | <QL | 4 | 3 | <QL | <QL | <QL |
| Silver | 97 | 17 | N/A | N/A | <QL | <QL | 17 | 17 | 17 | <QL | <QL |
| Ruthenium | 97 | 2 | N/A | N/A | 0.76 | <QL | 2 | 2 | <0.5 | 1 | <QL |
| Rhodium | 97 | 8 | N/A | N/A | 4.30 | <QL | 8 | 8 | 9 | 4 | <QL |
| Platinum | 97 | 1 | N/A | N/A | <QL | 0.1 | 1 | 1 | <0.5 | <0.5 | 0.1 |
| Palladium | 97 | 1 | N/A | N/A | <QL | <QL | 1 | 1 | <QL | <QL | <QL |
| Osmium | 97 | 1 | N/A | N/A | <QL | <QL | 1 | 1 | 1 | <QL | <QL |
| Iridium | 97 | 7 | N/A | N/A | 5.98 | <QL | 7 | 7 | 9 | 6 | <QL |
| Thallium | 78 | 5 | N/A | N/A | 3.59 | <QL | 5 | 5 | 6 | 4 | <QL |
| Cobalt | 48 | <0.5 | N/A | N/A | <QL | <QL | <0.5 | <0.5 | <QL | <0.5 | <QL |
| Lead | 48 | 6 | N/A | N/A | 5.01 | 1.6 | 6 | 6 | 6 | 5 | 1.5 |
| Mercury | 29 | 2 | N/A | N/A | 0.81 | 1 | 2 | 1 | 1 | 1 | 1.1 |
| Cadmium | 19 | 2 | N/A | N/A | 1.37 | <QL | 2 | 2 | 1 | 1 | <QL |

Table 22. (cont.) Elemental Impurity Leachables Results for L-Cysteine HCl Injection [X] (ppb)

| Element | AEC (ppb) | XMHJ1702B 25 °C/60 %RH | | | | | XMHJ1702B 40 °C/75 %RH | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Time point (months) | | | | | | | | | |
| | | 0 | 1 | 2 | 3 | 6 | 0 | 1 | 2 | 3 | 6 |
| Molybdenum | 14537 | 2 | N/A | N/A | 1 | 0.5 | 2 | 2 | <QL | 1 | 0.4 |
| Zinc | 12598 | 38 | N/A | N/A | 71 | 23.5 | 38 | 39 | <QL | 7 | 23.1 |
| Iron | 12598 | 166 | N/A | N/A | 31 | 7.9 | 166 | 35 | <QL | 16 | 12.3 |
| Chromium | 10660 | 9 | N/A | N/A | <QL | 2.1 | 9 | 6 | <QL | <QL | 1.9 |
| Barium | 6784 | 1 | N/A | N/A | <QL | <QL | 1 | 1 | <QL | <QL | <QL |
| Tin | 5815 | 3 | N/A | N/A | 21 | 1.5 | 3 | 4 | 3 | 3 | 1.3 |
| Copper | 2907 | 2 | N/A | N/A | <QL | <QL | 2 | 2 | <QL | <QL | 0.3 |
| Manganese | 2423 | 3 | N/A | N/A | <QL | 0.1 | 3 | 1 | <QL | <QL | 0.3 |
| Lithium | 2423 | 6 | N/A | N/A | 4 | 0.2 | 6 | 6 | <QL | 4 | 0.2 |
| Gold | 969 | 5 | N/A | N/A | 3 | 0.1 | 5 | 4 | 5 | 3 | 0.1 |
| Antimony | 872 | 2 | N/A | N/A | 1 | <QL | 2 | 2 | 1 | 1 | <QL |
| Selenium | 775 | 3 | N/A | N/A | <QL | 0.1 | 3 | 2 | <QL | <QL | <QL |
| Nickel | 194 | 10 | N/A | N/A | 9 | 8.2 | 10 | 8 | 4 | 8 | 8.2 |
| Arsenic | 174 | 2 | N/A | N/A | <QL | 0.3 | 2 | 2 | <QL | <QL | 0.1 |
| Aluminum | 120 | <QL | N/A | N/A | (6) <QL | <QL | <QL | (10) <QL | (25) <QL | (6) <QL | <QL |
| Vanadium | 97 | 4 | N/A | N/A | <QL | <QL | 4 | 4 | <QL | <QL | <QL |
| Silver | 97 | 17 | N/A | N/A | <QL | <QL | 17 | 17 | 17 | <QL | <QL |
| Ruthenium | 97 | 2 | N/A | N/A | 1 | <QL | 2 | 2 | <0.5 | 1 | <QL |
| Rhodium | 97 | 8 | N/A | N/A | 4 | <QL | 8 | 8 | 9 | 4 | <QL |
| Platinum | 97 | 1 | N/A | N/A | <0.5 | 0.1 | 1 | 1 | <0.5 | <0.5 | 0.1 |
| Palladium | 97 | 1 | N/A | N/A | <QL | <QL | 1 | 1 | <QL | <QL | <QL |
| Osmium | 97 | 1 | N/A | N/A | <QL | <QL | 1 | 1 | 1 | <QL | <QL |
| Iridium | 97 | 7 | N/A | N/A | 6 | <QL | 7 | 7 | 9 | 6 | <QL |
| Thallium | 78 | 5 | N/A | N/A | 4 | <QL | 5 | 5 | 6 | 4 | <QL |
| Cobalt | 48 | <0.5 | N/A | N/A | <0.5 | <QL | <0.5 | <0.5 | <QL | <0.5 | <QL |
| Lead | 48 | 6 | N/A | N/A | 5 | 1.5 | 6 | 6 | 6 | 5 | 1.5 |
| Mercury | 29 | 2 | N/A | N/A | 1 | 0.5 | 2 | 1 | 1 | 1 | 0.4 |
| Cadmium | 19 | 2 | N/A | N/A | 1 | <QL | 2 | 2 | 1 | 1 | <QL |

## Example 10

### Visual Inspection of Filled Vials

The L-Cysteine product that was manufactured by the two methods (i.e., lyophilzer chamber method and high-speed filler method) were inspected at after 1 month after production for visible signs of degradation in the form of visible particulate matter. In the presence of oxygen, two L-Cysteine residues will form a disulfide covalent bond forming L-Cystine. L-Cystine has a lower solubility (0.112 mg/mL) than L-Cysteine (50 mg/mL), in some cases the degradant can be visually observed.

Table 23. Comparison of Particulate Matter

| | PROT-000213 | XMHJ1705 | XMHJ1706 | XMHJ1707 |
|---|---|---|---|---|
| Total Vials | 1918 | 3473 | 3473 | 3497 |
| White PM | 36 | 120 | 31 | 32 |
| Overall % | 1.88% | 3.46% | 0.89% | 0.92% |

As the data show, no confirmed degradation was observed by either method indicating that the head space oxygen reduction and dissolved oxygen levels achieved herein are successful in producing L-Cysteine injection of desirable quality attributes.

All documents cited or referenced in the application cited documents, and all documents cited or referenced herein ("herein cited documents"), and all documents cited or referenced in herein cited documents, together with any manufacturer's instructions, descriptions, product specifications, and product sheets for any products mentioned herein or in any document incorporated by reference herein, are hereby incorporated herein by reference, and may be employed in the practice of the invention.

As used herein, "a," "an," or "the" can mean one or more than one. For example, "a" cell can mean a single cell or a multiplicity of cells.

Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

The term "consists essentially of" (and grammatical variants), as applied to the compositions of this invention, means the composition can contain additional components as long as the additional components do not materially alter the composition.

As used herein, the term "about" is used to provide flexibility to a numerical range endpoint by providing that a given value may be "a little above" or "a little below" the endpoint. Unless otherwise stated, use of the term "about" in accordance with a specific number or numerical range should also be understood to provide support for such

numerical terms or range without the term "about". For example, for the sake of convenience and brevity, a numerical range of "about 50 milligrams to about 80 milligrams" should also be understood to provide support for the range of "50 milligrams to 80 milligrams." Furthermore, it is to be understood that in this written description support for actual numerical values is provided even when the term "about" is used therewith. Furthermore, the term "about," as used herein when referring to a measurable value such as an amount of a compound or agent of this invention, dose, time, temperature, and the like, is meant to encompass variations of ±20%, ±10%, ±5%, ±1%, ±0.5%, or even ±0.1% of the specified amount. To be clear, the range encompassed by "about" will include all discrete values within that range, regardless of whether such discrete values are explicitly specified and/or prefaced by "about." Equivalents permissible for such discrete values as well as all ranges and subranges are within the scope of this disclosure.

Concentrations, amounts, and other numerical data may be expressed or presented herein in a range format. It is to be understood that such a range format is used merely for convenience and brevity and thus should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. As an illustration, a numerical range of "about 1 to about 5" should be interpreted to include not only the explicitly recited values of about 1 to about 5, but also include individual values and sub-ranges within the indicated range. Thus, included in this numerical range are individual values such as 2, 3, and 4 and sub-ranges such as from 1-3, from 2-4, and from 3-5, etc., as well as 1, 2, 3, 4, and 5, individually. This same principle applies to ranges reciting only one numerical value as a minimum or a maximum. Furthermore, such an interpretation should apply regardless of the breadth of the range or the characteristics being described.

Having thus described in detail preferred embodiments of the present invention, it is to be understood that the invention defined by the above paragraphs is not to be limited to particular details set forth in the above description as many apparent variations thereof are possible without departing from the spirit or scope of the present invention.

WHAT IS CLAIMED IS:

1. A solution of L-cysteine for use in total parenteral nutrition (TPN) comprising,

about 10 mg/mL to about 100 mg/mL of L-cysteine or a pharmaceutically acceptable salt or hydrate thereof, in a pharmaceutically acceptable carrier; wherein:

after 12 months of storage in a sealed vial at room temperature:

the total amount of oxygen within the sealed vial is no more than about 5%; and

the solution:

contains no more than 250 ppb aluminum,

is substantially free of visually detectable particulate matter, and

has a pH from 1.0 to 2.5.

2. The solution of claim 1, wherein after 12 months of storage in a sealed vial at room temperature, the total amount of oxygen within the sealed vial is no more than 4%.

3. The solution of claim 1, wherein after 12 months of storage in a sealed vial at room temperature, the solution contains no more than 150 ppb aluminum.

4. The solution of claim 1, wherein the vial is configured to substantially prevent atmospheric oxygen ingress and leaching of aluminum into the solution during storage of the solution in the vial.

5. A method of preparing the solution of claim 1 comprising,

applying an inert gas to the carrier to reduce the dissolved oxygen content in the carrier to no more than 2 ppm;

under an inert gas, mixing the carrier with L-cysteine hydrochloride monohydrate or a pharmaceutically acceptable L-cysteine or a salt or hydrate thereof;

optionally adjusting the pH of the mixture to from 1.0 to 2.5;

transferring an amount of the mixture into a vial;

overlaying the mixture with an inert gas; and

sealing the vial, wherein the headspace oxygen within the sealed vial is no more than 5%.

6. The method of claim 5, wherein the dissolved oxygen content in the carrier is reduced to no more than 1 ppm.

7. The method of claim 5, wherein the headspace oxygen within the sealed vial is no more than 4%.

8. The method of claim 5, wherein the dissolved oxygen content of the solution within the sealed vial is no more than 5 ppm.

9. The method of claim 5, wherein in transferring an amount of the mixture into a vial, an inert gas is utilized to minimize exposure of the solution to oxygen.

10. A solution of L-cysteine for use in total parenteral nutrition (TPN) comprising, about 10 mg/mL to about 100 mg/mL of L-cysteine or a pharmaceutically acceptable salt or hydrate thereof, in a pharmaceutically acceptable carrier; wherein:

after 18 months of storage in a sealed vial at room temperature:

the total amount of oxygen within the sealed vial is no more than about 5%; and

the solution:

contains no more than 250 ppb aluminum,

is substantially free of visually detectable particulate matter, and

has a pH from 1.0 to 2.5.

11. The solution of claim 10, wherein after 18 months of storage in a sealed vial at room temperature, the total amount of oxygen within the sealed vial is no more than 4%.

12. The solution of claim 10, wherein after 18 months of storage in a sealed vial at room temperature, the solution contains no more than 150 ppb aluminum.

13. The solution of claim 10, wherein the vial is configured to substantially prevent atmospheric oxygen ingress and leaching of aluminum into the solution during storage of the solution in the vial.

14. A method of preparing the solution of claim 10 comprising,

applying an inert gas to the carrier to reduce the dissolved oxygen content in the carrier to no more than 2 ppm;

under an inert gas, mixing the carrier with L-cysteine hydrochloride monohydrate or a pharmaceutically acceptable L-cysteine or a salt or hydrate thereof;

optionally adjusting the pH of the mixture to from 1.0 to 2.5;

transferring an amount of the mixture into a vial;

overlaying the mixture with an inert gas; and

sealing the vial, wherein the headspace oxygen within the sealed vial is no more than 5%.

15. The method of claim 14, wherein the dissolved oxygen content in the carrier is reduced to no more than 1 ppm.

16. The method of claim 14, wherein the headspace oxygen within the sealed vial is no more than 4%.

17. The method of claim 14, wherein the dissolved oxygen content of the solution within the sealed vial is no more than 5 ppm.

18. The method of claim 14, wherein in transferring an amount of the mixture into a vial, an inert gas is utilized to minimize exposure of the solution to oxygen.

19. A solution of L-cysteine for use in total parenteral nutrition (TPN) comprising, about 10 mg/mL to about 100 mg/mL of L-cysteine or equivalent amount of a pharmaceutically acceptable salt or hydrate thereof, in a pharmaceutically acceptable carrier; wherein:

after 24 months of storage in a sealed vial at room temperature:

the total amount of oxygen within the sealed vial is no more than about 5%; and

the solution:

contains no more than 250 ppb aluminum,

is substantially free of visually detectable particulate matter, and

has a pH from 1.0 to 2.5.

20. The solution of claim 19, wherein after 24 months of storage in a sealed vial at room temperature, the total amount of oxygen within the sealed vial is no more than 4%.

21. The solution of claim 19, wherein after 24 months of storage in a sealed vial at room temperature, the solution contains no more than 150 ppb aluminum.

22. The solution of claim 19, wherein the vial is configured to substantially prevent atmospheric oxygen ingress and leaching of aluminum into the solution during storage of the solution in the vial.

23. A method of preparing the solution of claim 19 comprising,

applying an inert gas to the carrier to reduce the dissolved oxygen content in the carrier to no more than 2 ppm;

under an inert gas, mixing the carrier with L-cysteine hydrochloride monohydrate or a pharmaceutically acceptable L-cysteine or a salt or hydrate thereof;

optionally adjusting the pH of the mixture to from 1.0 to 2.5;

transferring an amount of the mixture into a vial;

overlaying the mixture with an inert gas; and

sealing the vial, wherein the headspace oxygen within the sealed vial is no more than 5%.

24. The method of claim 23, wherein the dissolved oxygen content in the carrier is reduced to no more than 1 ppm.

25. The method of claim 23, wherein the headspace oxygen within the sealed vial is no more than 4%.

26. The method of claim 23, wherein the dissolved oxygen content of the solution within the sealed vial is no more than 5 ppm.

27. The method of claim 23, wherein in transferring an amount of the mixture into a vial, an inert gas is utilized to minimize exposure of the solution to oxygen.

28. The solution of claim 1, wherein the concentration of L-cysteine is about 34.5 mg/mL to about 50 mg/mL.

29. The solution of claim 10, wherein the concentration of L-cysteine is about 34.5 mg/mL to about 50 mg/mL.

30. The solution of claim 19, wherein the concentration of L-cysteine is about 34.5 mg/mL to about 50 mg/mL.

## ABSTRACT

The subject matter described herein is directed to stable L-cysteine compositions for injection, comprising: L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof in an amount from about 10 mg/mL to about 100 mg/mL; Aluminum in an amount from about 1.0 parts per billion (ppb) to about 250 ppb; cystine in an amount from about 0.01 wt% to about 2 wt% relative to L-cysteine; pyruvic acid in an amount from about 0.01 wt% to about 2 wt% relative to L-cysteine; a pharmaceutically acceptable carrier, comprising water; headspace $O_2$ that is less than 1.0%; dissolved oxygen present in the carrier in an amount from about 0.01 parts per million (ppm) to about 1 ppm, wherein the composition is enclosed in a single-use container having a volume of from 10 mL to 100 mL. Also described are compositions for a total parenteral nutrition regimen and methods for their use.

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 066859/589619 |
|---|---|---|
| | Application Number | |
| Title of Invention | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE | |

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
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☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 066859/589619 |
|---|---|---|
| | Application Number | |
| Title of Invention | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE | |

| City | Waxhaw | State/Province | NC | Country of Residence | US |
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## Application Information:

| | | | |
|---|---|---|---|
| Title of the Invention | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE | | |
| Attorney Docket Number | 066859/589619 | Small Entity Status Claimed | ☐ |
| Application Type | Nonprovisional | | |
| Subject Matter | Utility | | |
| Total Number of Drawing Sheets (if any) | 5 | Suggested Figure for Publication (if any) | |

## Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

| Application number of the previously filed application | Filing date (YYYY-MM-DD) | Intellectual Property Authority or Country |
|---|---|---|
| | | |

## Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☒ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 066859/589619 |
|---|---|---|
| | Application Number | |
| Title of Invention | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE | |

## Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

| Please Select One: | ● Customer Number | US Patent Practitioner | ◯ Limited Recognition (37 CFR 11.9) |
|---|---|---|---|
| Customer Number | 826 | | |

## Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

| Prior Application Status | Pending | | | Remove |
|---|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) | |
| | Continuation of | 17/950964 | 2022-09-22 | |

| Prior Application Status | Patented | | | Remove |
|---|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing Date (YYYY-MM-DD) | Patent Number | Issue Date (YYYY-MM-DD) |
| 17/950964 | Continuation of | 17/188922 | 2021-03-01 | 11510942 | 2022-11-29 |

| Prior Application Status | Patented | | | Remove |
|---|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing Date (YYYY-MM-DD) | Patent Number | Issue Date (YYYY-MM-DD) |
| 17/188922 | Continuation of | 16/746028 | 2020-01-17 | 10933089 | 2021-03-02 |

| Prior Application Status | Patented | | | Remove |
|---|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing Date (YYYY-MM-DD) | Patent Number | Issue Date (YYYY-MM-DD) |
| 16/746028 | Continuation of | 16/665702 | 2019-10-28 | 10583155 | 2020-03-10 |

| Prior Application Status | Patented | | | Remove |
|---|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing Date (YYYY-MM-DD) | Patent Number | Issue Date (YYYY-MM-DD) |
| 16/665702 | Continuation of | 16/248460 | 2019-01-15 | 10478453 | 2019-11-19 |

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

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## Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

| Application Number | Country[i] | Filing Date (YYYY-MM-DD) | Access Code[i] (if applicable) |
|---|---|---|---|
| | | | |

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

## Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

PTO/AIA/14 (01-22)
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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 066859/589619 |
|---|---|---|
| | Application Number | |
| Title of Invention | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE | |

## Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

**NOTE**: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

**1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)**

**A. Priority Document Exchange (PDX)** - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

**B. Search Results from U.S. Application to EPO** - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

**2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)**

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

**NOTE:** Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (01-22)
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|---|---|---|
| | Application Number | |
| Title of Invention | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE | |

## Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

**Applicant 1** Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

| ● Assignee | Legal Representative under 35 U.S.C. 117 | Joint Inventor |
|---|---|---|
| Person to whom the inventor is obligated to assign. | Person who shows sufficient proprietary interest | |

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

| Organization Name | EXELA PHARMA SCIENCES, LLC | | |
|---|---|---|---|
| **Mailing Address Information For Applicant:** | | | |
| **Address 1** | 1245 BLOWING ROCK BLVD | | |
| Address 2 | | | |
| **City** | LENOIR | **State/Province** | NC |
| **Country** | US | Postal Code | 28645 |
| Phone Number | | Fax Number | |
| Email Address | | | |

Additional Applicant Data may be generated within this form by selecting the Add button. Add

## Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (01-22)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 066859/589619 |
|---|---|---|
| | Application Number | |
| Title of Invention | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE | |

**Assignee 1**

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

| Organization Name | EXELA PHARMA SCIENCES, LLC |
|---|---|

**Mailing Address Information For Assignee including Non-Applicant Assignee:**

| **Address 1** | 1245 BLOWING ROCK BLVD | | |
|---|---|---|---|
| Address 2 | | | |
| **City** | LENOIR | **State/Province** | NC |
| **Country** i | US | Postal Code | 28645 |
| Phone Number | | Fax Number | |
| Email Address | | | |

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

## Signature:

Remove

**NOTE:** This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

| **Signature** | /BRYAN L. SKELTON/ | | | Date (YYYY-MM-DD) | 2022-12-16 |
|---|---|---|---|---|---|
| First Name | BRYAN L. | Last Name | SKELTON | Registration Number | |

Additional Signature may be generated within this form by selecting the Add button. Add

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 066859/589619 |
|---|---|---|
| | Application Number | |
| Title of Invention | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE | |

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

# Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NUMBER | FILING or 371(c) DATE | GRP ART UNIT | FIL FEE REC'D | ATTY.DOCKET.NO | TOT CLAIMS | IND CLAIMS |
|---|---|---|---|---|---|---|
| 18/067,287 | 12/16/2022 | | 2820 | 066859/589619 | 30 | 3 |

**CONFIRMATION NO. 9793**

826
ALSTON & BIRD LLP
ONE SOUTH AT THE PLAZA
101 SOUTH TRYON STREET
SUITE 4000
CHARLOTTE, NC 28280-4000

**FILING RECEIPT**

*OC000000052539523*

Date Mailed: 01/13/2023

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

**Please verify the accuracy of the data presented on this receipt.** If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

**Inventor(s)**

John Maloney, Salisbury, NC;
Aruna Koganti, Lenoir, NC;
Phanesh Koneru, Waxhaw, NC;

**Applicant(s)**

EXELA PHARMA SCIENCES, LLC, LENOIR, NC;

**Assignment For Published Patent Application**

EXELA PHARMA SCIENCES, LLC, LENOIR, NC

**Power of Attorney:** The patent practitioners associated with Customer Number 00826

**Domestic Priority data as claimed by applicant**

This application is a CON of 17/950,964 09/22/2022
which is a CON of 17/188,922 03/01/2021 PAT 11,510,942
which is a CON of 16/746,028 01/17/2020 PAT 10,933,089
which is a CON of 16/665,702 10/28/2019 PAT 10,583,155
which is a CON of 16/248,460 01/15/2019 PAT 10,478,453

**Foreign Applications** for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
*Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.*

**Permission to Access Application via Priority Document Exchange:** Yes

**Permission to Access Search Results:** Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

**If Required, Foreign Filing License Granted:** 01/10/2023

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/067,287**

**Projected Publication Date:** Request for Non-Publication Acknowledged

**Non-Publication Request:** Yes

**Early Publication Request:** No

**Title**

STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE

**Preliminary Class**

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

## PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

## LICENSE FOR FOREIGN FILING UNDER

## Title 35, United States Code, Section 184

## Title 37, Code of Federal Regulations, 5.11 & 5.15

**GRANTED**

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

**NOT GRANTED**

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

---

## *SelectUSA*

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor

community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

## PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 18/067,287

### APPLICATION AS FILED - PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY FEE($) |
|---|---|---|---|---|---|---|---|
| BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | | | N/A | 320 |
| SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | | | N/A | 700 |
| EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | | | N/A | 800 |
| TOTAL CLAIMS (37 CFR 1.16(i)) | 30 minus 20 = | * 10 | | | OR | x 100 = | 1000 |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | 3 minus 3 = | * | | | | x = | 0 |
| APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | | | | 0 |
| MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | | | | 0 |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | TOTAL | | | TOTAL | 1820 |

### APPLICATION AS AMENDED - PART II

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY ADDITIONAL FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT A | Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE($) | ADDITIONAL FEE($) | | RATE($) | ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT B | Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/067,287 | 12/16/2022 | John Maloney | 066859/589619 | 9793 |

826 7590 02/15/2023

ALSTON & BIRD LLP
ONE SOUTH AT THE PLAZA
101 SOUTH TRYON STREET
SUITE 4000
CHARLOTTE, NC 28280-4000

| EXAMINER |
|---|
| CENTRAL, DOCKET |

| ART UNIT | PAPER NUMBER |
|---|---|
| OPAP | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 02/15/2023 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

usptomail@alston.com

| *Decision Granting Request for Prioritized Examination (Track I)* | **Application No.** 18/067,287 | **Applicant(s)** Maloney et al. | |
|---|---|---|---|
| | **Examiner** FIKIRTE A GEREMEW | **Art Unit** OMBL | **AIA (FITF) Status** Yes |

1. THE REQUEST FILED 16 December 2022 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☑ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to FIKIRTE GEREMEW at (703) 756-1930. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

| /FIKIRTE A GEREMEW/<br>PROGRAM SUPPORT ASSISTANT, OMBL | |
|---|---|

Substitute for form 1449B/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 1 of 22

| *Complete if Known* | |
|---|---|
| Application Number | 18/067,287 |
| Filing Date | 12-16-2022 |
| First Named Inventor | John Maloney |
| Art Unit | 1612 |
| Examiner Name | Benjamin J. Packard |
| Attorney Docket Number | 066859/589619 |

**U.S. PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Document Number<br>Number Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
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| Examiner Signature | | Date Considered | |
|---|---|---|---|

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

**Submitted: February 27, 2023**

| Substitute for form 1449B/PTO | | | | Complete if Known | |
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| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** | | | | Application Number | 18/067,287 |
| | | | | Filing Date | 12-16-2022 |
| | | | | First Named Inventor | John Maloney |
| | | | | Art Unit | 1612 |
| *(Use as many sheets as necessary)* | | | | Examiner Name | Benjamin J. Packard |
| Sheet | 2 | of | 22 | Attorney Docket Number | 066859/589619 |

| NON PATENT LITERATURE DOCUMENTS | | | |
|---|---|---|---|
| Examiner Initials * | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T [2] |
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| | | | | Art Unit | 1612 |
| *(Use as many sheets as necessary)* | | | | Examiner Name | Benjamin J. Packard |
| Sheet | 3 | of | 22 | Attorney Docket Number | 066859/589619 |

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| | | | | Art Unit | 1612 |
| *(Use as many sheets as necessary)* | | | | Examiner Name | Benjamin J. Packard |
| Sheet | 4 | of | 22 | Attorney Docket Number | 066859/589619 |

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| Sheet | 5 | of | 22 | Attorney Docket Number | 066859/589619 |

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| Examiner Signature | | Date Considered | |
|---|---|---|---|

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| | | | | First Named Inventor | John Maloney |
| | | | | Art Unit | 1612 |
| *(Use as many sheets as necessary)* | | | | Examiner Name | Benjamin J. Packard |
| Sheet | 6 | of | 22 | Attorney Docket Number | 066859/589619 |

| | | | |
|---|---|---|---|
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**Submitted: February 27, 2023**

| Substitute for form 1449B/PTO | | | | Complete if Known | |
|---|---|---|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** | | | | Application Number | 18/067,287 |
| | | | | Filing Date | 12-16-2022 |
| | | | | First Named Inventor | John Maloney |
| | | | | Art Unit | 1612 |
| *(Use as many sheets as necessary)* | | | | Examiner Name | Benjamin J. Packard |
| Sheet | 19 | of | 22 | Attorney Docket Number | 066859/589619 |

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| | | | | Art Unit | 1612 |
| *(Use as many sheets as necessary)* | | | | Examiner Name | Benjamin J. Packard |
| Sheet | 20 | of | 22 | Attorney Docket Number | 066859/589619 |

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| | | | | Filing Date | 12-16-2022 |
| | | | | First Named Inventor | John Maloney |
| | | | | Art Unit | 1612 |
| *(Use as many sheets as necessary)* | | | | Examiner Name | Benjamin J. Packard |
| Sheet | 22 | of | 22 | Attorney Docket Number | 066859/589619 |

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**Submitted: February 27, 2023**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| In re: | John Maloney et al. | Confirmation No.: | 9793 |
| Appl. No.: | 18/067,287 | Group Art Unit: | 1612 |
| Filed: | December 16, 2022 | Examiner: | Benjamin J. Packard |
| For: | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE | | |

Submitted via EFS-Web
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**INFORMATION DISCLOSURE STATEMENT**
**CITATION UNDER 37 C.F.R. § 1.97**

Attached is a list of documents on form PTO-SB08.

Copies of all listed documents (other than U.S. patents, U.S. patent application publications, or patents or publications otherwise determined cumulative) are attached, except those (if any) that were previously submitted to, or cited by, the Office during the prosecution of any application(s) upon which the present application directly relies for an earlier effective filing date under 35 U.S.C. § 120. It is noted that 37 C.F.R. § 1.98(d) establishes that copies of documents previously submitted to, or cited by, the Office during prosecution of the above application(s) are not required to be furnished; however, copies of such documents will be furnished upon request.

Also attached is a translation or a concise explanation of each non-English language document.

It is requested that the Examiner consider these documents and officially make them of record in accordance with the provisions of 37 C.F.R. § 1.97 and Section 609 of the MPEP. By identifying the listed documents, Applicant in no way makes any admission as to the prior art status of the listed documents but is instead identifying the listed documents for the sake of full disclosure.

In accordance with 37 C.F.R. § 1.98(d) the above application(s) are properly identified in the table below:

| Application No. | Filing Date | Pub./Patent No. | Status |
|---|---|---|---|
| 17/950,964 | 09-22-2022 | | Allowed |
| 17/188,922 | 03-01-2021 | 11,510,942 | Issued |
| 16/746,028 | 01-17-2020 | 10,933,089 | Issued |
| 16/665,702 | 10-28-2019 | 10,583,155 | Issued |
| 16/248,460 | 01-15-2019 | 10,478,453 | Issued |

Respectfully submitted,

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# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **18/067,287** | **02/27/2023 03:33:46 PM ET** | **066859/589619** |

## Title of Invention

STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 9793 | FILED BY | LaKeisha Robinson Preddie |
| PATENT CENTER # | 61656686 | FILING DATE | 12/16/2022 |
| CUSTOMER # | 826 | FIRST NAMED INVENTOR | John Maloney |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Bryan Skelton |

## Documents

**TOTAL DOCUMENTS: 2**

| DOCUMENT | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|
| 589619 IDS SB08AB.pdf | 22 | Information Disclosure Statement (IDS) Form (SB08) | 580 KB |
| Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems. | | | |
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## Digest

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| 589619 IDS SB08AB.pdf | 01BE5FFE79C20607DD11EB6341F8B1ED6EF396735767D75EE B4A0B8CEE4FE8272ABF242E5081103BE0B8EEE4BF33455F2E 0BA543595CADDFB22D476356089021 |
| 589619 IDS Transmittal.pdf | 7F79D6657792A4B311B693D82260E13F3E2C761A7483D2DBB4 589CEFE2277C81CFF8A9AF9CDFACA97D68CF5C52C273376C E34B03009FB4E7B3F7238B4D1DBB9D |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/067,287 | 12/16/2022 | John Maloney | 066859/589619 | 9793 |

826 7590 03/08/2023

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| EXAMINER | |
|---|---|
| PACKARD, BENJAMIN J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1612 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 03/08/2023 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

usptomail@alston.com

| *Office Action Summary* | Application No. 18/067,287 | Applicant(s) Maloney et al. | |
|---|---|---|---|
| | Examiner BENJAMIN J PACKARD | Art Unit 1612 | AIA (FITF) Status Yes |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5) ☑ Claim(s) 1-30 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-30 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 22pgs (2/27/23).

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

**DETAILED ACTION**

***Notice of Pre-AIA or AIA Status***

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

**Claims 1-30** are rejected on the ground of nonstatutory double patenting as being unpatentable over claims of U.S. Patent No. 10,905,713, U.S. Patent No. 10,933,089, U.S. Patent No. 10,583,155, U.S. Patent No. 10,478,453, U.S. Patent No. 11,510,942, U.S. Patent No. 11,510,942. Although the claims at issue are not identical, they are not patentably distinct from each other because the patents are all directed to compositions and stored compositions of L-cysteine having low levels of aluminum over extended periods with pH values below 2.5 and substantially free of visually detectable particulate matter. Further, where the compositions are taught to be parenteral compositions, it would have been obvious to administer the composition to patients in need thereof, given the fact that a parenteral is a route of administration, and to optimize the dosing regimen to the specific patients' populations disclosed.

**Claims 1-30** are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over the claims of copending Application No. 17/950,979 (allowed by not issued), 17/950,922 (allowed by not issued), 18/067,397, 18/067,605 (reference applications). Although the claims at issue are not identical, they are not patentably distinct from each other because the copending application is directed to compositions and stored compositions of L-cysteine having low levels of aluminum over extended periods with pH values below 2.5 and substantially free of visually detectable

particulate matter over various periods of time. Further, where the compositions are taught to be parenteral compositions, it would have been obvious to administer the composition to patients in need thereof, given the fact that a parenteral is a route of administration, and to optimize the dosing regimen to the specific patients' populations disclosed. Finally, it would have been obvious to optimize the stability over various time periods in order to maximize shelf life before use.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BENJAMIN J PACKARD whose telephone number is (571)270-3440. The examiner can normally be reached Mon and Wed-Fri (8am-6pm).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like

assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BENJAMIN J PACKARD/
Primary Examiner, Art Unit 1612

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/067,287 | Maloney et al. |
| | Examiner | Art Unit |
| | BENJAMIN J PACKARD | 1612 |

| CPC - Searched* | | |
|---|---|---|
| Symbol | Date | Examiner |
| A61K 33/06 | 03/02/2023 | BP |

| CPC Combination Sets - Searched* | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| US Classification - Searched* | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| | | | |

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| Search Notes | | |
|---|---|---|
| Search Notes | Date | Examiner |
| Palm invetor search | 03/02/2023 | BP |
| PE2P search | 03/02/2023 | BP |
| Google scholar search, terms: l-cysteine, aluminum, impurity, stability , parenteral | 03/02/2023 | BP |

| Interference Search | | | |
|---|---|---|---|
| US Class/CPC Symbol | US Subclass/CPC Group | Date | Examiner |
| | | | |

## PE2E SEARCH - Search History (Prior Art)

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | British Equivalents | Time Stamp |
|---|---|---|---|---|---|---|---|
| L1 | 24789 | l-cysteine aluminum | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | AND | ON | ON | 2023/03/02 01:45 PM |
| L2 | 2285 | l-cysteine.clm. aluminum | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | AND | ON | ON | 2023/03/02 01:45 PM |
| L3 | 73 | l-cysteine.clm. (aluminum WITH less WITH than) | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | AND | ON | ON | 2023/03/02 01:45 PM |
| L4 | 28 | l-cysteine.clm. (aluminum WITH impurity) | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, | AND | ON | ON | 2023/03/02 01:45 PM |

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|---|---|---|---|---|---|---|---|
| | | | CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | | | | |
| L5 | 54 | (L3 OR L4) AND @py<="2019" | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | AND | ON | ON | 2023/03/02 01:46 PM |

## PE2E SEARCH - Search History (Interference)

| |
|---|
| There are no Interference searches to show. |

Substitute for form 1449B/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 1 of 22

| *Complete if Known* | |
|---|---|
| Application Number | 18/067,287 |
| Filing Date | 12-16-2022 |
| First Named Inventor | John Maloney |
| Art Unit | 1612 |
| Examiner Name | Benjamin J. Packard |
| Attorney Docket Number | 066859/589619 |

**U.S. PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Document Number<br>Number Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
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| Examiner Signature | /BENJAMIN J PACKARD/ | Date Considered | 03/02/2023 |
|---|---|---|---|

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

**Submitted: February 27, 2023**

LEGAL02/42592197v1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.J.P/

| Substitute for form 1449B/PTO | | | | Complete if Known | |
|---|---|---|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** | | | | Application Number | 18/067,287 |
| | | | | Filing Date | 12-16-2022 |
| | | | | First Named Inventor | John Maloney |
| | | | | Art Unit | 1612 |
| *(Use as many sheets as necessary)* | | | | Examiner Name | Benjamin J. Packard |
| Sheet | 2 | of | 22 | Attorney Docket Number | 066859/589619 |

| NON PATENT LITERATURE DOCUMENTS | | | |
|---|---|---|---|
| Examiner Initials * | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T [2] |
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| Examiner Signature | /BENJAMIN J PACKARD/ | Date Considered | 03/02/2023 |
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*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

**Submitted: February 27, 2023**



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| | | | | Filing Date | 12-16-2022 |
| | | | | First Named Inventor | John Maloney |
| | | | | Art Unit | 1612 |
| *(Use as many sheets as necessary)* | | | | Examiner Name | Benjamin J. Packard |
| Sheet | 3 | of | 22 | Attorney Docket Number | 066859/589619 |

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| Examiner Signature | /BENJAMIN J PACKARD/ | Date Considered | 03/02/2023 |
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**Submitted: February 27, 2023**



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| *(Use as many sheets as necessary)* | | | | Examiner Name | Benjamin J. Packard |
| Sheet | 4 | of | 22 | Attorney Docket Number | 066859/589619 |

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| | | | | Filing Date | 12-16-2022 |
| | | | | First Named Inventor | John Maloney |
| | | | | Art Unit | 1612 |
| *(Use as many sheets as necessary)* | | | | Examiner Name | Benjamin J. Packard |
| Sheet | 22 | of | 22 | Attorney Docket Number | 066859/589619 |

| | | | |
|---|---|---|---|
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| | 308 | ZIEGLER, EKHARD E., "Parenteral Nutrition," Iowa Neonatology Handbook: Feeding, (2006). | |
| | 207 | ZLOTKIN et al., "Cysteine supplementation to cysteine-free intravenous feeding regimens in newborn infants," The American Journal of Clinical Nutrition, 34(5):914-923, (1981). [Retrieved from the Internet April 14, 2015: <URL: https://academic.oup.com/ajcn/article-abstract/34/5/914/4431066>]. | |
| | 208 | ZLOTKIN et al., "The Development of Cystathionase Activity During the First Year of Life," Pediatr. Res., 16(1):65-68, (1982). | |

| Examiner Signature | /BENJAMIN J PACKARD/ | Date Considered | 03/02/2023 |
|---|---|---|---|

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

**Submitted: February 27, 2023**



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.J.P/

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | |
|---|---|---|
| Appl. No.: | 18/067,287 | Confirmation No.: 9793 |
| Applicant(s): | John Maloney et al. | |
| Filed: | December 16, 2022 | |
| Art Unit: | 1612 | |
| Examiner: | BENJAMIN J PACKARD | |
| Title: | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE | |

Docket No.: 066859/589619
Customer No.: 826

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**RESPONSE TO OFFICE ACTION UNDER 37 C.F.R. 1.111**

In response to the Office Action dated March 8, 2023, and concurrent with the filing of a Terminal Disclaimer pursuant to 37 C.F.R. § 1.321, please reconsider the above-identified application in view of the **Remarks** beginning on page 2 of this paper.

## REMARKS

### I. Status of Claims

Claims 1-30 remain unchanged and pending in this application for reconsideration.

### II. Nonstatutory Double Patenting Rejections Are Overcome

The Office Action rejects claims 1-30 on the ground of nonstatutory double patenting for allegedly being unpatentable over the claims in U.S. Patent Nos. 10,905,713; 10,933,089; 10,583,155; 10,478,453; 11,510,941[1] and 11,510,942. Without acquiescing to any rationale set forth in the Office Action and solely to place this application in condition for allowance, Applicant submits herewith a terminal disclaimer referencing U.S. Patent Nos. 10,905,713; 10,933,089; 10,583,155; 10,478,453; 11,510,941 and 11,510,942.

The Office Action provisionally rejects claims 1-30 on the ground of nonstatutory double patenting for allegedly being unpatentable over the claims in U.S. Patent Application Nos. 17/950,979; 17/950,964[2]; 18/067,397 and 18/067,605. Without acquiescing to any rationale set forth in the Office Action and solely to place this application in condition for allowance, Applicant submits herewith a terminal disclaimer referencing U.S. Patent Application Nos. 17/950,979; 17/950,964; 18/067,397 and 18/067,605. Thus, the provisional nonstatutory double patenting rejection of claims 1-30 in the instant application is moot.

[1] To be clear, Applicant notes that this patent is listed as 11,510,942 in the Office Action, but believes this is a minor typographical clerical error.

[2] To be clear, Applicant notes that this patent application is listed as 17/950,922 in the Office Action, but believes this is a minor typographical clerical error.

## CONCLUSION

Having addressed all the issues set forth in the Office Action, the present application is now in condition for allowance. Should there be any issue that impedes the allowance of any claim, the Examiner is invited to telephone Applicant's undersigned representative so that the issue may be resolved expeditiously.

Applicant does not believe that any extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time or fees are necessary to allow consideration of this paper, Applicant hereby petitions such extensions of time under 37 C.F.R. § 1.136(a) and authorizes any required fees (including any fees for net addition of claims) to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

/Bryan L. Skelton/

Bryan L. Skelton
Registration No. 50,893

**Customer No. 826**
**ALSTON & BIRD LLP**
104 South Tryon Street
Suite 4000,Charlotte
NC 28280-4000
Tel Research Triangle Park Office (919) 862-2200
Fax Research Triangle Park Office Office (919) 862-2260

**ELECTRONICALLY FILED USING THE EFS-WEB ELECTRONIC FILING SYSTEM OF THE UNITED STATES PATENT & TRADEMARK OFFICE ON March 8, 2023.**

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 47651098 |
| **Application Number:** | 18067287 |
| **International Application Number:** | |
| **Confirmation Number:** | 9793 |
| **Title of Invention:** | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE |
| **First Named Inventor/Applicant Name:** | John Maloney |
| **Customer Number:** | 826 |
| **Filer:** | Bryan Lee Skelton/Raquel West |
| **Filer Authorized By:** | Bryan Lee Skelton |
| **Attorney Docket Number:** | 066859/589619 |
| **Receipt Date:** | 08-MAR-2023 |
| **Filing Date:** | 16-DEC-2022 |
| **Time Stamp:** | 16:02:59 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 589619_reply.pdf | 116980<br>d5a35b15c40ad10edfa76d026ca604ac37a5b3f8 | yes | 3 |

| | Multipart Description/PDF files in .zip description | | |
|---|---|---|---|
| | **Document Description** | **Start** | **End** |
| | Amendment/Request for Reconsideration-After Non-Final Rejection | 1 | 1 |
| | Applicant Arguments/Remarks Made in an Amendment | 2 | 3 |
| **Warnings:** | | | |
| **Information:** | | | |
| | **Total Files Size (in bytes):** | 116980 | |

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**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**
**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**
**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

| | |
|---|---|
| **Doc Code: DIST.E.FILE**<br>**Document Description: Electronic Terminal Disclaimer - Filed** | PTO/SB/25<br>PTO/SB/26<br>U.S. Patent and Trademark Office<br>Department of Commerce |

| | |
|---|---|
| Electronic Petition Request | **TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION AND TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT** |
| Application Number | 18067287 |
| Filing Date | 16-Dec-2022 |
| First Named Inventor | John Maloney |
| Attorney Docket Number | 066859/589619 |
| Title of Invention | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE |

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

| Owner | Percent Interest |
|---|---|
| EXELA PHARMA SCIENCES, LLC | 100 % |

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

17950979 filed on 09/22/2022

17950964 filed on 09/22/2022

18067397 filed on 12/16/2022

18067605 filed on 12/16/2022

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

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10478453

10583155

10933089

10905713

11510942

11510941

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicants claims the following fee status:

○ Small Entity

○ Micro Entity

◉ Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

- (●) An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

  Registration Number 50893

- ( ) A sole inventor
- ( ) A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application
- ( ) A joint inventor; all of whom are signing this request

| | |
|---|---|
| Signature | /Bryan L. Skelton/ |
| Name | Bryan L. Skelton |

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 18067287 |
| **Filing Date:** | 16-Dec-2022 |
| **Title of Invention:** | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE |
| **First Named Inventor/Applicant Name:** | John Maloney |
| **Filer:** | Bryan Lee Skelton/Raquel West |
| **Attorney Docket Number:** | 066859/589619 |

Filed as Large Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| STATUTORY OR TERMINAL DISCLAIMER | 1814 | 1 | 170 | 170 |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Extension-of-Time:** | | | | |
| **Miscellaneous:** | | | | |
| | | | **Total in USD ($)** | **170** |

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 18067287

Filing Date: 16-Dec-2022

Applicant/Patent under Reexamination: Maloney

Electronic Terminal Disclaimer filed on March 8, 2023

☒ APPROVED

**This patent is subject to a terminal disclaimer**

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 47651268 |
| **Application Number:** | 18067287 |
| **International Application Number:** | |
| **Confirmation Number:** | 9793 |
| **Title of Invention:** | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE |
| **First Named Inventor/Applicant Name:** | John Maloney |
| **Customer Number:** | 826 |
| **Filer:** | Bryan Lee Skelton/Raquel West |
| **Filer Authorized By:** | Bryan Lee Skelton |
| **Attorney Docket Number:** | 066859/589619 |
| **Receipt Date:** | 08-MAR-2023 |
| **Filing Date:** | 16-DEC-2022 |
| **Time Stamp:** | 16:10:49 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | DA |
| Payment was successfully received in RAM | $170 |
| RAM confirmation Number | E202338G10445366 |
| Deposit Account | 160605 |
| Authorized User | Raquel West |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>37 CFR 1.16 (National application filing, search, and examination fees)<br>37 CFR 1.17 (Patent application and reexamination processing fees) | |

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Terminal Disclaimer-Filed (Electronic) | eTerminal-Disclaimer.pdf | 51006<br>78403ce4947e8f50133afa55c49bf8057b29ecad | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Fee Worksheet (SB06) | fee-info.pdf | 38121<br>d68c7bf77e557a0d995ce81219b26d1debd6464c | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
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**New Applications Under 35 U.S.C. 111**
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**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**
**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

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# NOTICE OF ALLOWANCE AND FEE(S) DUE

826 7590 03/22/2023

ALSTON & BIRD LLP
ONE SOUTH AT THE PLAZA
101 SOUTH TRYON STREET
SUITE 4000
CHARLOTTE, NC 28280-4000

| EXAMINER | |
|---|---|
| PACKARD, BENJAMIN J | |
| ART UNIT | PAPER NUMBER |
| 1612 | |

DATE MAILED: 03/22/2023

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/067,287 | 12/16/2022 | John Maloney | 066859/589619 | 9793 |

TITLE OF INVENTION: STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | UNDISCOUNTED | $1200 | $0.00 | $0.00 | $1200 | 06/22/2023 |

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

**HOW TO REPLY TO THIS NOTICE:**

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

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If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

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II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

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PTOL-85 (Rev. 02/11)

## PART B - FEE(S) TRANSMITTAL

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By fax, send to: (571)-273-2885

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826 7590 03/22/2023

ALSTON & BIRD LLP
ONE SOUTH AT THE PLAZA
101 SOUTH TRYON STREET
SUITE 4000
CHARLOTTE, NC 28280-4000

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

| |
|---|
| (Typed or printed name) |
| (Signature) |
| (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/067,287 | 12/16/2022 | John Maloney | 066859/589619 | 9793 |

TITLE OF INVENTION: STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | UNDISCOUNTED | $1200 | $0.00 | $0.00 | $1200 | 06/22/2023 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| PACKARD, BENJAMIN J | 1612 | 424-621000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
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1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/067,287 | 12/16/2022 | John Maloney | 066859/589619 | 9793 |

826 7590 03/22/2023

ALSTON & BIRD LLP
ONE SOUTH AT THE PLAZA
101 SOUTH TRYON STREET
SUITE 4000
CHARLOTTE, NC 28280-4000

| EXAMINER | |
|---|---|
| PACKARD, BENJAMIN J | |
| ART UNIT | PAPER NUMBER |
| 1612 | |

DATE MAILED: 03/22/2023

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

## OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

## Privacy Act Statement

**The Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

| Notice of Allowability | Application No. 18/067,287 | Applicant(s) Maloney et al. | |
|---|---|---|---|
| | Examiner BENJAMIN J PACKARD | Art Unit 1612 | AIA (FITF) Status Yes |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--*

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 3/8/23.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-30 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   **Certified copies:**

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 2pgs (2/27/23).
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/BENJAMIN J PACKARD/
Primary Examiner, Art Unit 1612

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/067,287 | Maloney et al. |
| | Examiner | Art Unit |
| | BENJAMIN J PACKARD | 1612 |

| CPC | | | | | | |
|---|---|---|---|---|---|---|
| Symbol | | | | | Type | Version |
| A61K | / | 33 | / | 06 | F | 2013-01-01 |
| A23L | / | 33 | / | 16 | I | 2016-08-01 |
| A61K | / | 31 | / | 191 | I | 2013-01-01 |
| A61K | / | 9 | / | 0029 | I | 2013-01-01 |
| A61K | / | 31 | / | 405 | I | 2013-01-01 |
| A61K | / | 31 | / | 095 | I | 2013-01-01 |
| A23L | / | 33 | / | 175 | I | 2016-08-01 |
| A61K | / | 31 | / | 198 | I | 2013-01-01 |
| A61K | / | 31 | / | 4172 | I | 2013-01-01 |
| A61K | / | 31 | / | 401 | I | 2013-01-01 |
| A61K | / | 33 | / | 28 | I | 2013-01-01 |
| A61K | / | 33 | / | 241 | I | 2019-01-01 |
| A61K | / | 33 | / | 36 | I | 2013-01-01 |
| A61K | / | 33 | / | 00 | I | 2013-01-01 |
| A61K | / | 47 | / | 02 | I | 2013-01-01 |
| A23V | / | 2002 | / | 00 | A | 2013-01-01 |
| A61J | / | 1 | / | 1412 | A | 2013-01-01 |

| CPC Combination Sets | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Symbol | | | | | Type | Set | Ranking | Version |
| | / | | / | | | | | |

| NONE | | Total Claims Allowed: | |
|---|---|---|---|
| (Assistant Examiner) | (Date) | 30 | |
| /BENJAMIN J PACKARD/<br>Primary Examiner, Art Unit 1612 | 17 March 2023 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | 1 |

U.S. Patent and Trademark Office — Part of Paper No.: 20230317

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/067,287 | Maloney et al. |
| | Examiner | Art Unit |
| | BENJAMIN J PACKARD | 1612 |

| INTERNATIONAL CLASSIFICATION | | | | |
|---|---|---|---|---|
| CLAIMED | | | | |
| A61K | / | 33 | / | 06 |

| NON-CLAIMED | | | | |
|---|---|---|---|---|
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| US ORIGINAL CLASSIFICATION | |
|---|---|
| CLASS | SUBCLASS |
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| CROSS REFERENCES(S) | | | | | | |
|---|---|---|---|---|---|---|
| CLASS | SUBCLASS (ONE SUBCLASS PER BLOCK) | | | | | |
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| NONE<br>(Assistant Examiner) | (Date) | Total Claims Allowed: 30 | |
|---|---|---|---|
| /BENJAMIN J PACKARD/<br>Primary Examiner, Art Unit 1612<br>(Primary Examiner) | 17 March 2023<br>(Date) | O.G. Print Claim(s)<br>1 | O.G. Print Figure<br>1 |

U.S. Patent and Trademark Office — Part of Paper No.: 20230317

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/067,287 | Maloney et al. |
| | **Examiner** | **Art Unit** |
| | BENJAMIN J PACKARD | 1612 |

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

**CLAIMS**

| Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original |
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| NONE | | **Total Claims Allowed:** | |
|---|---|---|---|
| (Assistant Examiner) | (Date) | 30 | |
| /BENJAMIN J PACKARD/<br>Primary Examiner, Art Unit 1612 | 17 March 2023 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | 1 |

U.S. Patent and Trademark Office Part of Paper No.: 20230317

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/067,287 | Maloney et al. |
| | Examiner | Art Unit |
| | BENJAMIN J PACKARD | 1612 |

| CPC - Searched* | | |
|---|---|---|
| **Symbol** | **Date** | **Examiner** |
| A61K 33/06 | 03/02/2023 | BP |
| A61K 33/06 | 03/17/2023 | BP |

| CPC Combination Sets - Searched* | | |
|---|---|---|
| **Symbol** | **Date** | **Examiner** |
| | | |

| US Classification - Searched* | | | |
|---|---|---|---|
| **Class** | **Subclass** | **Date** | **Examiner** |
| | | | |

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| Search Notes | | |
|---|---|---|
| **Search Notes** | **Date** | **Examiner** |
| Palm invetor search | 03/02/2023 | BP |
| PE2P search | 03/02/2023 | BP |
| Google scholar search, terms: l-cysteine, aluminum, impurity, stability , parenteral | 03/02/2023 | BP |
| PE2P search | 03/17/2023 | BP |
| Google scholar search, terms: l-cysteine, aluminum, impurity, stability , parenteral | 03/17/2023 | BP |

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/067,287 | Maloney et al. |
| | Examiner | Art Unit |
| | BENJAMIN J PACKARD | 1612 |

| Interference Search | | | |
|---|---|---|---|
| US Class/CPC Symbol | US Subclass/CPC Group | Date | Examiner |
| A61K | 33/06 | 03/17/2023 | BP |

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 18/067,287 | Maloney et al. |
| | Examiner | Art Unit |
| | BENJAMIN J PACKARD | 1612 |

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|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

**CLAIMS**

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
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| Final | Original | 03/17/2023 | | | | | | | | |
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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| In re: | John Maloney et al. | Confirmation No.: | 9793 |
| Appl. No.: | 18/067,287 | Group Art Unit: | 1612 |
| Filed: | December 16, 2022 | Examiner: | Benjamin J. Packard |
| For: | STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE | | |

Submitted via EFS-Web
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**INFORMATION DISCLOSURE STATEMENT**
**CITATION UNDER 37 C.F.R. § 1.97**

Attached is a list of documents on form PTO-SB08.

Copies of all listed documents (other than U.S. patents, U.S. patent application publications, or patents or publications otherwise determined cumulative) are attached, except those (if any) that were previously submitted to, or cited by, the Office during the prosecution of any application(s) upon which the present application directly relies for an earlier effective filing date under 35 U.S.C. § 120. It is noted that 37 C.F.R. § 1.98(d) establishes that copies of documents previously submitted to, or cited by, the Office during prosecution of the above application(s) are not required to be furnished; however, copies of such documents will be furnished upon request.

Also attached is a translation or a concise explanation of each non-English language document.

It is requested that the Examiner consider these documents and officially make them of record in accordance with the provisions of 37 C.F.R. § 1.97 and Section 609 of the MPEP. By identifying the listed documents, Applicant in no way makes any admission as to the prior art status of the listed documents but is instead identifying the listed documents for the sake of full disclosure.



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.J.P/

In accordance with 37 C.F.R. § 1.98(d) the above application(s) are properly identified in the table below:

| Application No. | Filing Date | Pub./Patent No. | Status |
|---|---|---|---|
| 17/950,964 | 09-22-2022 | | Allowed |
| 17/188,922 | 03-01-2021 | 11,510,942 | Issued |
| 16/746,028 | 01-17-2020 | 10,933,089 | Issued |
| 16/665,702 | 10-28-2019 | 10,583,155 | Issued |
| 16/248,460 | 01-15-2019 | 10,478,453 | Issued |

Respectfully submitted,

/bryan l. skelton/

Bryan L. Skelton
Registration No. 50,893

**Customer No. 826**
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Fax Research Triangle Area Office (919) 862-2260

03/17/2023

/BENJAMIN J PACKARD/



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.J.P/

## PE2E SEARCH - Search History (Prior Art)

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | British Equivalents | Time Stamp |
|---|---|---|---|---|---|---|---|
| L1 | 42946 | A61K33/06.cpc. | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | AND | ON | ON | 2023/03/17 12:37 PM |
| L2 | 6460 | L1 AND aluminum | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | AND | ON | ON | 2023/03/17 12:37 PM |
| L3 | 821 | L2 AND cysteine | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | AND | ON | ON | 2023/03/17 12:38 PM |
| L4 | 153 | L3 AND cysteine.clm. | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, | AND | ON | ON | 2023/03/17 12:39 PM |

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## PE2E SEARCH - Search History (Interference)

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | British Equivalents | Time Stamp |
|---|---|---|---|---|---|---|---|
| N1 | 4466 | A61K33/06.cpc. | (US-PGPUB; USPAT) | AND | ON | ON | 2023/03/17 12:37 PM |
| N2 | 440 | n1 AND aluminum.clm. | (US-PGPUB; USPAT) | AND | ON | ON | 2023/03/17 12:38 PM |
| N3 | 0 | N2 AND cycsteine.clm. | (US-PGPUB; USPAT) | AND | ON | ON | 2023/03/17 12:38 PM |
| N4 | 19 | N2 AND cysteine.clm. | (US-PGPUB; USPAT) | AND | ON | ON | 2023/03/17 12:38 PM |

## Bibliographic Data

Application No: 18/067,287

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /BENJAMIN J PACKARD/ Examiner's Signature | Initials

Title: STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE

| FILING or 371(c) DATE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 12/16/2022 | 424 | 1612 | 066859/589619 |
| RULE | | | |

**APPLICANTS**

EXELA PHARMA SCIENCES, LLC, LENOIR, NC, UNITED STATES

**INVENTORS**

John Maloney, Salisbury, NC, UNITED STATES

Aruna Koganti, Lenoir, NC, UNITED STATES

Phanesh Koneru, Waxhaw, NC, UNITED STATES

**CONTINUING DATA**

This application is a CON of 17950964 09/22/2022

17950964 is a CON of 17188922 03/01/2021 PAT 11510942

17188922 is a CON of 16746028 01/17/2020 PAT 10933089

16746028 is a CON of 16665702 10/28/2019 PAT 10583155

16665702 is a CON of 16248460 01/15/2019 PAT 10478453

**FOREIGN APPLICATIONS**

**IF REQUIRED, FOREIGN LICENSE GRANTED****

01/10/2023

**STATE OR COUNTRY**

UNITED STATES

**ADDRESS**

ALSTON & BIRD LLP
ONE SOUTH AT THE PLAZA
101 SOUTH TRYON STREET
SUITE 4000
CHARLOTTE, NC 28280-4000
UNITED STATES

**FILING FEE RECEIVED**

$7,160

## PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

826 7590 03/22/2023

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101 SOUTH TRYON STREET
SUITE 4000
CHARLOTTE, NC 28280-4000

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**Certificate of Mailing or Transmission**

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

| | |
|---|---|
| Raquel West | (Typed or printed name) |
| /Raquel West/ | (Signature) |
| March 23, 2023 | (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/067,287 | 12/16/2022 | John Maloney | 066859/589619 | 9793 |

TITLE OF INVENTION: STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | UNDISCOUNTED | $1200 | $0.00 | $0.00 | $1200 | 06/22/2023 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| PACKARD, BENJAMIN J | 1612 | 424-621000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Alston & Bird LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: EXELA PHARMA SCIENCES, LLC

(B) RESIDENCE: (CITY and STATE OR COUNTRY): LENOIR, NORTH CAROLINA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ☒ Corporation or other private group entity ❑ Government

4a. Fees submitted: ☒ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 160605

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Bryan L. Skelton/ Date March 23, 2023

Typed or printed name Bryan L. Skelton Registration No. 50893



PTOL-85 Part B (08-18) Approved for use through 01/31/2020 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES
PATENT AND TRADEMARK OFFICE

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# ELECTRONIC PAYMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| 18/067,287 | 03/23/2023 07:08:51 PM ET | 066859/589619 |

## Title of Invention

STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 9793 | FILED BY | Raquel West |
| PATENT CENTER # | 61798065 | AUTHORIZED BY | Bryan Skelton |
| CUSTOMER # | 826 | FILING DATE | 12/16/2022 |
| CORRESPONDENCE ADDRESS | - | FIRST NAMED INVENTOR | John Maloney |

## Payment Information

| PAYMENT METHOD | PAYMENT TRANSACTION ID | PAYMENT AUTHORIZED BY |
|---|---|---|
| DA / 160605 | E20233MJ09327915 | Raquel West |

| PRE-AUTHORIZED ACCOUNT | PRE-AUTHORIZED CATEGORY |
|---|---|
| 160605 | 37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges) |

| FEE CODE | DESCRIPTION | ITEM PRICE($) | QUANTITY | ITEM TOTAL($) |
|---|---|---|---|---|
| 1501 | UTILITY ISSUE FEE | 1200.00 | 1 | 1200.00 |
| | | | TOTAL AMOUNT: | $1,200.00 |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement

Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **18/067,287** | **03/23/2023 07:08:51 PM ET** | **066859/589619** |

## Title of Invention

STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 9793 | FILED BY | Raquel West |
| PATENT CENTER # | 61798065 | FILING DATE | 12/16/2022 |
| CUSTOMER # | 826 | FIRST NAMED INVENTOR | John Maloney |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Bryan Skelton |

## Documents

**TOTAL DOCUMENTS: 1**

| DOCUMENT | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|
| 589619_IF.pdf | 1 | Issue Fee Payment (PTO-85B) | 124 KB |

## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| 589619_IF.pdf | C49DE9A3B17EDCA6931492CD6E4ECDE11B53574F6EE7E557<br>C91EB741315C16F8C535C2C828B68D1D1E895776F7FDF2194<br>91F74A55F0DAF435B06E5016F116295 |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as

described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

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Alexandria, Virginia 22313-1450
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| APPLICATION NO. | ISSUE DATE | PATENT NO. | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 18/067,287 | 05/09/2023 | 11642370 | 066859/589619 | 9793 |

826 7590 04/19/2023

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CHARLOTTE, NC 28280-4000

# ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PAIR WEB site http://pair.uspto.gov for additional inventors):

John Maloney, Salisbury, NC;
Aruna Koganti, Lenoir, NC;
Phanesh Koneru, Waxhaw, NC;

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

EXELA PHARMA SCIENCES, LLC, LENOIR, NC;

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Alexandria, VA 22313-1450
www.uspto.gov

| APPLICATION NO. | ISSUE DATE | PATENT NO. |
|---|---|---|
| 18/067,287 | 09-MAY-23 | 11642370 |

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1120 SOUTH TRYON STREET SUITE 300
CHARLOTTE, NC 28203-6818

## EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at https://patentcenter.uspto.gov

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit https://www.uspto.gov/electronicgrants