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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):	
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 January 15, 2019
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.

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

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.

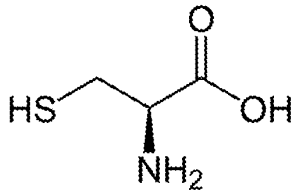
Additionally, controlling heat in the process including during the compounding and/or sterilization activities, unexpectedly was found to be beneficial for preparing stable L-Cysteine compositions described herein. This was surprising because L-Cysteine has been used in parenteral products as an excipient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

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
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 yrs to 17 yrs	10.66 to 20	0.007 to 0.012	0.017 to 0.029	0.04 to 0.07	0.05 to 0.088
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) 16th 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. 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" 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 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 Head Space Gas Analysis	Dissolved Oxygen =Report Value 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 Head Space Gas Analysis	Dissolved Oxygen =Report Value 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	1.590
Sample 3	-	0.565	1.522
Sample 4	-	0.550	1.447
Average	**10.57%**	**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-0000055 Study Empty Vials Avg.			1.150
PROT-0000055 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 Low High	2.3 % Oxygen N/A N/A	1.9 % Oxygen N/A N/A	1.9 % Oxygen N/A N/A	0.4 % Oxygen 0.2% Oxygen 0.5% Oxygen
1 Month Room Temperature	0.9 % Oxygen	2.8 % Oxygen	1.2 % Oxygen	1.1 % Oxygen (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: L-Cystine Pyruvic Acid Total Specified RRT-1.98 Individual Unspecified Total Impurities	 0.3% 0.1% 0.2% ND 0.5%	 0.3% 0.2% 0.2% ND 0.7%	 0.3% 0.1% 0.2% ND 0.6%
Dissolved Oxygen	(1) 0.12 ppm (2) 0.13 ppm	(1) 0.13 ppm (2) 0.14 ppm	(1) 0.14 ppm (2) 0.13 ppm
Head-Space Oxygen	(1) 0.16% (2) 0.37%	(1) 0.53% (2) 0.89%	(1) 0.56% (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

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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 °C/60 %RH**				**XMHJ1705 40 °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 °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 °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 °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 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 oxygen that is from about 0.5% v/v to 4.0% v/v 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 claim 1, wherein the composition is essentially free of an antioxidant.

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

4. The composition of claim 1, wherein said Aluminum is present in an amount from about 1.0 ppb to about 150 ppb.

5. The composition of claim 1, wherein said Aluminum is present in an amount from about 1.0 ppb to about 100 ppb.

6. The composition of claim 1, wherein said Aluminum is present in an amount from about 1.0 ppb to about 50 ppb.

7. The composition of claim 1, wherein said Aluminum is present in an amount from about 1.0 ppb to about 20 ppb.

8. The composition of claim 1, wherein the composition 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, wherein the total amount of Aluminum is from about 4.0 ppb to about 250 ppb.

9. The composition of claim 1, wherein said L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof is present in an amount from about 20 mg/mL to about 70 mg/mL.

10. The composition of claim 1, wherein said L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof is present in an amount from about 30 mg/mL to about 70 mg/mL.

11. The composition of claim 1, wherein said L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof is present in an amount of about 37.5 mg/mL.

12. The composition of claim 1, wherein said headspace oxygen is from about 2.0% v/v to about 4.0% v/v.

13. The composition of claim 1, wherein said headspace oxygen is from about 3.0% v/v to about 4.0% v/v.

14. The composition of claim 1, further comprising one or more heavy metals selected from the group consisting of Lead, Nickel, Arsenic and Mercury.

15. A total parenteral nutrition composition for parenteral administration, comprising an admixture of:

about 0.5 mL to about 10 mL an L-cysteine composition 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 10 ppb to about 80 ppb;

L-cystine in an amount from about 0.0.1 wt% to about 2.0 wt% relative to L-cysteine;

pyruvic acid in an amount from about 0.0.1 wt% to about 2.0 wt% relative to L-cysteine;

a pharmaceutically acceptable carrier, comprising water;

headspace oxygen that is from about 0.5% v/v to 4.0% v/v 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,

and, about 1 gram to 200 grams of an amino acid 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.

16. The composition of claim 15, where said L-cysteine composition and said amino acid composition are present in the admixture at a ratio of from about 1:50 to 1:1000.

17. The composition of claim 15, 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;

From about 10 mg/g amino acid to about 80 mg/g of 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

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

18. The composition of claim 17, wherein said L-cysteine is present at about 30 mg/g to about 50 mg/g of total amino acid content.

19. The composition of claim 17, wherein said L-cysteine is present at about 40 mg/g of total amino acid content.

20. The composition of claim 15, having a volume of about 100 mL to about 1000 mL for infusion within about 24 hours to about 48 hours of admixture.

21. A method of preparing the composition of claim 1, 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;

Filling said mixture into containers of use;

Reducing head space oxygen in said containers of use; and

Sealing said containers of use, wherein the dissolved oxygen in said containers of use is about 0.1 ppm to about 5 ppm.

22. A method of preparing a reduced Aluminum composition for 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.

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.

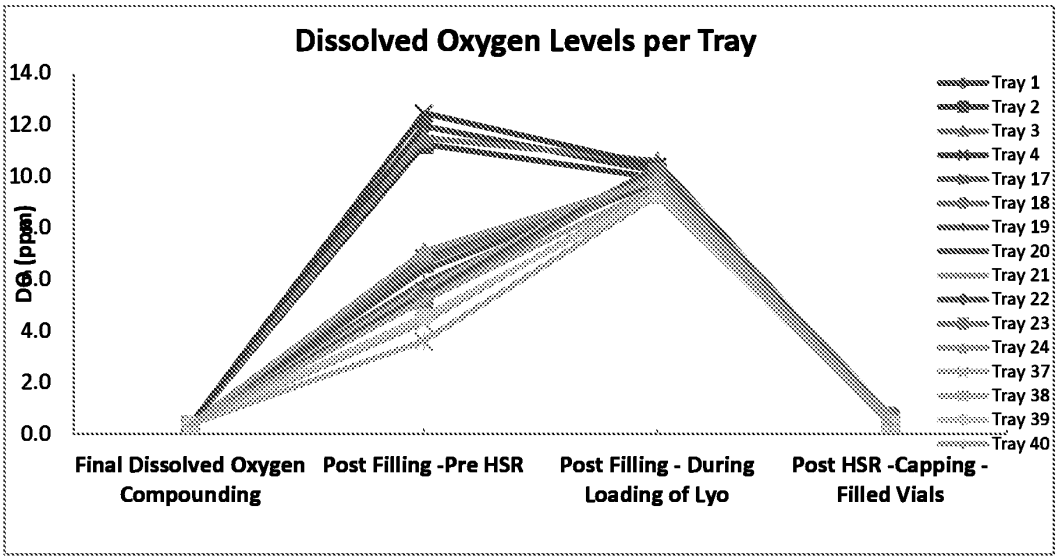
Dissolved Oxygen Levels per Tray
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
DO (ppm)
Final Dissolved Oxygen Compounding
Post Filling -Pre HSR
Post Filling - During Loading of Lyo
Post HSR -Capping - Filled Vials
Tray 1
Tray 2
Tray 3
Tray 4
Tray 17
Tray 18
Tray 19
Tray 20
Tray 21
Tray 22
Tray 23
Tray 24
Tray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

FIG. 1

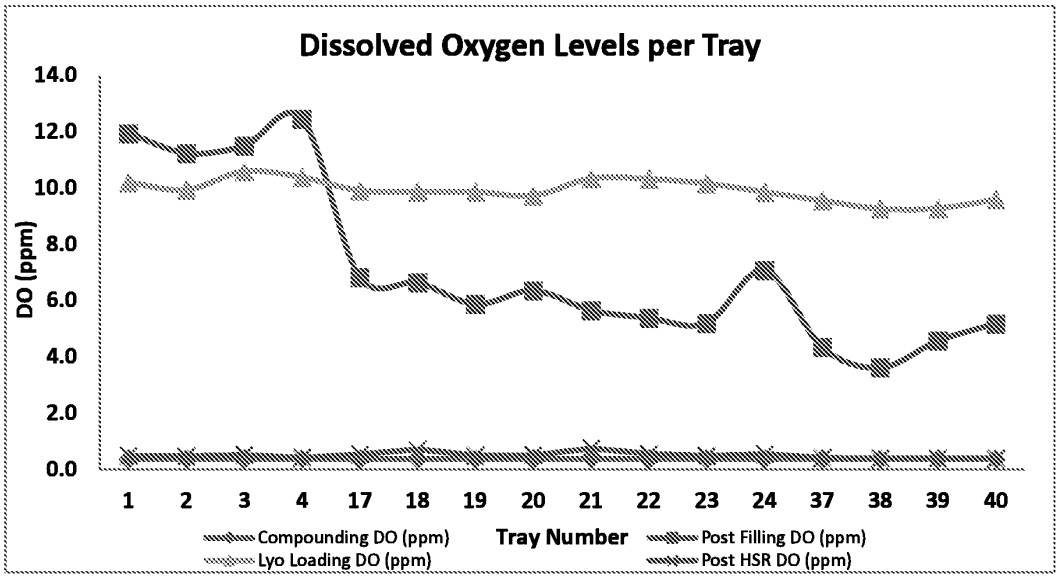
Dissolved Oxygen Levels per Tray
DO (ppm)
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
1
2
3
4
17
18
19
20
21
22
23
24
37
38
39
40
Tray Number
Compounding DO (ppm)
Lyo Loading DO (ppm)
Post Filling DO (ppm)
Post HSR DO (ppm)

FIG. 2

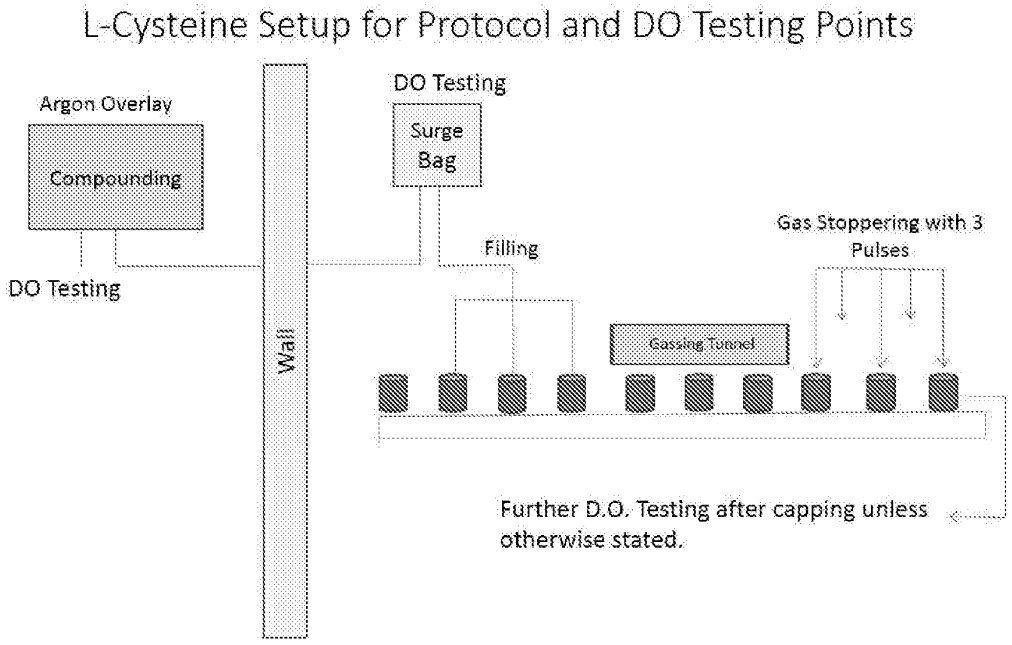
L-Cysteine Setup for Protocol and DO Testing Points
Argon Overlay
Compounding
DO Testing
DO Testing
Surge
Bag
Filling
Wall
Gassing Tunnel
Gas Stoppering with 3
Pulses
Further D.O. Testing after capping unless
otherwise stated.

FIG. 3

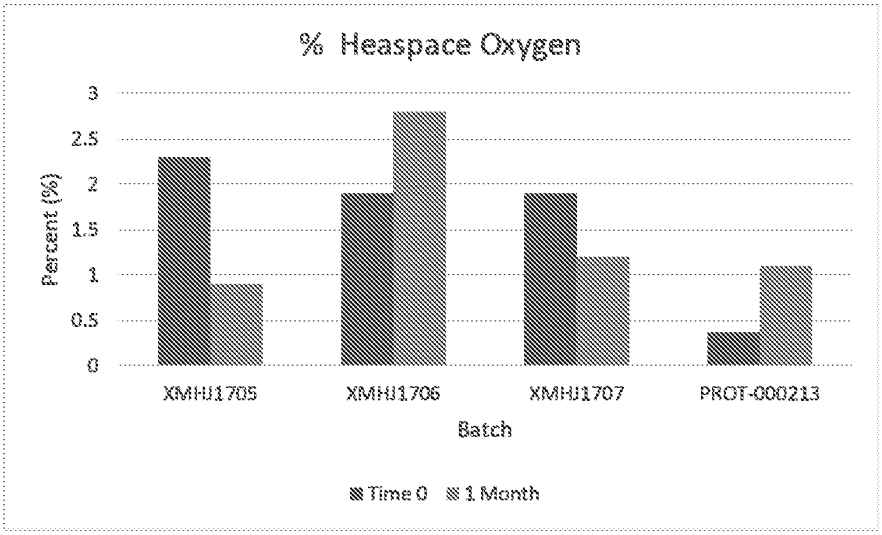
% Heaspace Oxygen
Percent (%)
3
2.5
2
1.5
1
0.5
0
XMHJ1705
XMHJ1706
XMHJ1707
PROT-000213
Batch
Time 0
1 Month

FIG. 4

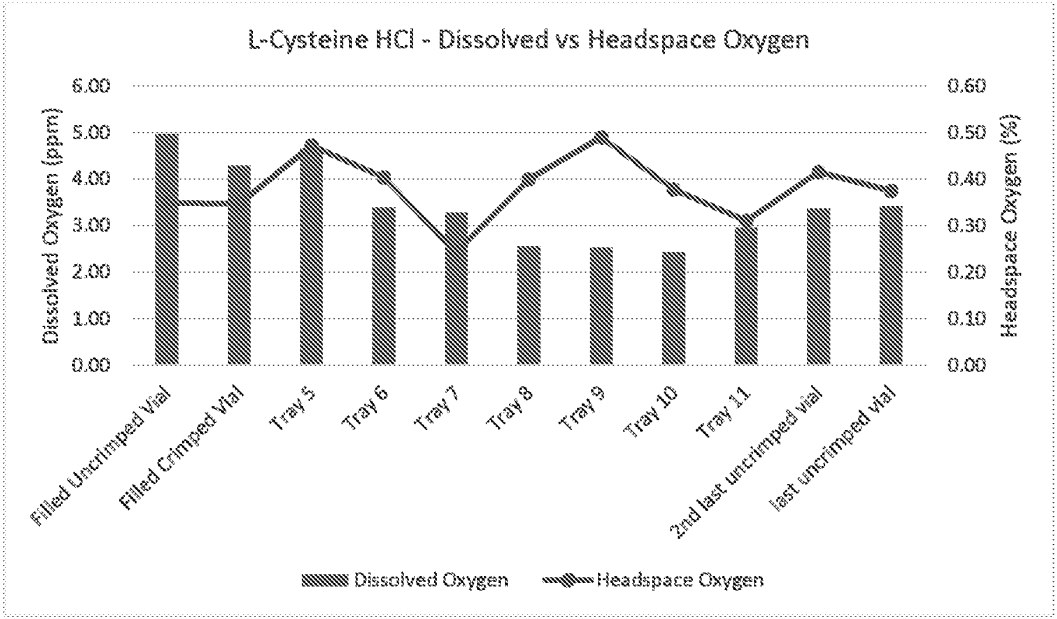
L-Cysteine HCl - Dissolved vs Headspace Oxygen
Dissolved Oxygen (ppm)
Headspace Oxygen (%)
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Filled Uncrimped Vial
Filled Crimped Vial
Tray 5
Tray 6
Tray 7
Tray 8
Tray 9
Tray 10
Tray 11
2nd last uncrimped vial
last uncrimped vial
Dissolved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

FIG. 5

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
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/Laura Tremont
Attorney Docket Number:	066859/509450

Filed as Large Entity

Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	300	300
UTILITY SEARCH FEE	1111	1	660	660
UTILITY EXAMINATION FEE	1311	1	760	760
REQUEST FOR PRIORITIZED EXAMINATION	1817	1	4000	4000
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	2	100	200
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**6060**

Electronic Acknowledgement Receipt

EFS ID:	34863196
Application Number:	16248460
International Application Number:	
Confirmation Number:	6641
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/Laura Tremont
Filer Authorized By:	Bryan Lee Skelton
Attorney Docket Number:	066859/509450
Receipt Date:	15-JAN-2019
Filing Date:	
Time Stamp:	17:33:52
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$6060
RAM confirmation Number	011619INTEFSW00005188160605
Deposit Account	160605
Authorized User	Laura Tremont
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 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)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	509450_ADS.pdf	148551 823c5f8e9343133489279afcd3dfd5a3f584cbca	no	9
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
2	TrackOne Request	509450_Track_One_Request.pdf	123012 62730aecc22190f072226b0215db839455b048dd	no	2
Warnings:					
Information:					
3		509450_Application_Text.pdf	532195 e30567578a2b4579f0cdba7c9e99a391f23051ea	yes	92

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	86
Claims	87	91
Abstract	92	92

Warnings:					
Information:					
4	Drawings-other than black and white line drawings	509450_Figures.pdf	211638 284f301199297318b853f79c61224e8b8292a9a6	no	5
Warnings:					
Information:					

5	Fee Worksheet (SB06)	fee-info.pdf	41716 60546aade4bf2dd33d7b74a32e17637dd9fa2743	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	1057112	

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 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.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	066859/509450
	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.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ 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.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	John		Maloney	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Lenoir	State/Province	NC	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Exela Pharma Sciences, LLC
Address 2	1245 Blowing Rock Blvd

City	Lenoir	State/Province	NC
Postal Code	28645	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Aruna		Koganti	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Lenoir	State/Province	NC	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Exela Pharma Sciences, LLC
Address 2	1245 Blowing Rock Blvd

City	Lenoir	State/Province	NC
Postal Code	28645	Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Phanesh		Koneru	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	066859/509450
	Application Number	
Title of Invention	STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE	

City	Lenoir	State/Province	NC	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Exela Pharma Sciences, LLC		
Address 2	1245 Blowing Rock Blvd		
City	Lenoir	**State/Province**	NC
Postal Code	28645	**Country**	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	00826		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE		
Attorney Docket Number	066859/509450	**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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	066859/509450
	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	00826		

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			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)

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

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) 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.

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

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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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	066859/509450
	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 (02-18)
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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	066859/509450
	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

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.

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 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	066859/509450
	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.

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

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country[i]		Postal Code	
Phone Number		Fax Number	
Email Address			

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

Signature:

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)	2019-01-15
First Name	Bryan L.	Last Name	Skelton	Registration Number	50893

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

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Approved for use through 11/30/2020. OMB 0651-0032
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	066859/509450
	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.

Doc Code: PA..
Document Description: Power of Attorney

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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	16/248,460
Filing Date	January 15, 2019
First Named Inventor	John Maloney
Title	STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE
Art Unit	1615
Examiner Name	Not yet assigned
Attorney Docket Number	066859/509450

SIGNATURE of Applicant or Patent Practitioner

Signature	/bryan l. skelton/	Date (Optional)	January 24, 2019
Name	Bryan L. Skelton	Registration Number	50893
Title (if Applicant is a juristic entity)	Patent Practitioner		
Applicant Name (if Applicant is a juristic entity)	Exela Pharma Sciences, LLC		

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

☑ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 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, 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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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	[signature]	Date (Optional)	
Name	PHANESH KONERU		
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.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 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, 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Patent Application Fee Transmittal

Application Number:	16248460
Filing Date:	
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/Laura Tremont
Attorney Docket Number:	066859/509450

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
LATE FILING FEE FOR OATH OR DECLARATION	1051	1	160	160
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Electronic Acknowledgement Receipt

EFS ID:	34949483
Application Number:	16248460
International Application Number:	
Confirmation Number:	6641
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/Laura Tremont
Filer Authorized By:	Bryan Lee Skelton
Attorney Docket Number:	066859/509450
Receipt Date:	24-JAN-2019
Filing Date:	
Time Stamp:	14:58:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$160
RAM confirmation Number	012519INTEFSW00001483160605
Deposit Account	160605
Authorized User	Laura Tremont
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 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)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	509450_Supplemental_ADS.pdf	21156 94d01b51fb4208e3661c87f2dc7762a66bd9996d	no	3
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
2	Transmittal Letter	509450_Transmittal_Letter.pdf	20061 5c71d3da5962c8b123565402d2a0f42254a7bcb3	no	2
Warnings:					
Information:					
3	Oath or Declaration filed	509450_Declarations.pdf	1475148 2fbd6150f24d55993c2334e3dc15c0154b9778bc	no	3
Warnings:					
Information:					
4	Power of Attorney	509450_POA.pdf	907549 36bbf67c0b18cf9c92c3099c473a2a20c70fdff4	no	2
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30351 c3178bcde1f18dbf08e34c64df0f2cfa0b5f429b	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2454265		

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 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.

Supplemental Application Data Sheet

Application Information

Application number:	16/248,460
Filing Date:	January 15, 2019
Application Type:	Nonprovisional
Subject Matter:	Utility
Title:	STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE
Attorney Docket Number:	066859/509450
Suggested Drawing Figure:	
Total Drawing Sheets:	5
Small Entity?:	No

Inventor Information

Inventor 1

Status:	Full Capacity
Given Name:	John
Middle Name:	
Family Name:	Maloney
Name Suffix:	
US Residency:	Yes
Non US Residency:	
Active US Military Service:	
City of Residence:	~~Lenoir~~ Salisbury
State or Province of Residence:	NC
Country of Residence:	US
Street of Mailing Address:	c/o Exela Pharma Sciences, LLC
Address 2:	1245 Blowing Rock Blvd
City of Mailing Address:	Lenoir
State or Province of mailing address:	NC
Country of mailing address:	US

Postal or Zip Code of mailing address:	28645

Inventor 2

Status:	Full Capacity
Given Name:	Aruna
Middle Name:	
Family Name:	Koganti
Name Suffix:	
US Residency:	Yes
Non US Residency:	
Active US Military Service:	
City of Residence:	Lenoir
State or Province of Residence:	NC
Country of Residence:	US
Street of Mailing Address:	c/o Exela Pharma Sciences, LLC
Address 2:	1245 Blowing Rock Blvd
City of Mailing Address:	Lenoir
State or Province of mailing address:	NC
Country of mailing address:	US
Postal or Zip Code of mailing address:	28645

Inventor 3

Status:	Full Capacity
Given Name:	Phanesh
Middle Name:	
Family Name:	Koneru
Name Suffix:	
US Residency:	Yes
Non US Residency:	
Active US Military Service:	
City of Residence:	~~Lenoir~~ Waxhaw
State or Province of Residence:	NC
Country of Residence:	US
Street of Mailing Address:	c/o Exela Pharma Sciences, LLC

Address 2:	1245 Blowing Rock Blvd
City of Mailing Address:	Lenoir
State or Province of mailing address:	NC
Country of mailing address:	US
Postal or Zip Code of mailing address:	28645

Submitted by:

Signature	/bryan l. skelton/	Date	2019-01-24
Printed Name	Bryan L. Skelton	Registration Number	50,893

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Exela Pharma Sciences, LLC	Conf. No. 6641
U.S. Appl. No.	16/248,460	
Filing Date:	01/15/2019	
Art Unit:	1615	
Examiner:	To be assigned	
Title:	STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE	

Docket No.: 066859/509450
Customer No.: 00826

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

TRANSMITTAL ACCOMPANYING SUPPLEMENTAL ADS

Sir:

Submitted concurrently herewith is a Supplemental Application Data Sheet to update the cities of residence listed for inventors John Maloney and Phanesh Koneru to "Salisbury, NC" and "Waxhaw, NC", respectively. Applicant requests that a Filing Receipt be issued reflecting the updated inventor residence information.

Also submitted concurrently herewith are inventor declarations for the above-referenced application. Applicant notes that authorization to charge the late declaration surcharge to Deposit Account No. 16-0605 was provided with the application filed January 15, 2019, and such fee is hereby additionally authorized to be charged to Deposit Account No. 16-0605 herewith.

Respectfully submitted,

/bryan l. skelton/

Bryan L. Skelton
Registration No. 50,893

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Research Triangle Area Office (919) 862-2200
Fax Research Triangle Area Office (919) 862-2260

ELECTRONICALLY FILED USING THE EFS-WEB ELECTRONIC FILING SYSTEM OF THE UNITED STATES PATENT & TRADEMARK OFFICE ON JANUARY 24, 2019.

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.

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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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WARNING:

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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.

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
16/248,460	01/15/2019	1615	2080	066859/509450	22	3

CONFIRMATION NO. 6641

FILING RECEIPT

826
ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

OC000000105884396

Date Mailed: 02/07/2019

Receipt is acknowledged of this non-provisional 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 APPLICANT, 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 Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections 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**

Inventor(s)

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

Applicant(s)

Exela Pharma Sciences, LLC, Lenoir, NC

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

Domestic Applications for which benefit is claimed - None.
A proper domestic benefit claim must be provided in an Application Data Sheet in order to constitute a claim for domestic benefit. See 37 CFR 1.76 and 1.78.

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: 02/06/2019

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/248,460**

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

424

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).

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/248,460

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	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	22 minus 20 =	* 2			OR	x 100 =	200
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x 460 =	0.00
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).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1920

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($)	ADDITIONAL FEE($)	OR	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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/248,460	01/15/2019	John Maloney	066859/509450

CONFIRMATION NO. 6641

826
ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

FORMALITIES LETTER

OC000000105684397

Date Mailed: 02/07/2019

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- A substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required. The substitute specification must be submitted with markings and be accompanied by a clean version (without markings) as set forth in 37 CFR 1.125(c) and a statement that the substitute specification contains no new matter (see 37 CFR 1.125(b)). The specification, claims, and/or abstract page(s) submitted is not acceptable and cannot be scanned or properly stored because:
  - The application papers (including any electronically submitted papers) are not in compliance with 37 CFR 1.52 because pages 15 -16, 19, 66 - 68, 70 - 71 contain text that is unreadable or of insufficient clarity. Application papers (including any electronically submitted papers) must be presented in a form having sufficient clarity and contrast between the background of the paper and the writing thereon to permit the Office to electronically reproduce the papers by use of digital imaging and optical character recognition. See 37 CFR 1.52(a)(1)(v).

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/sibrahim/

Attorney's Docket No. 066859/509450 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Exela Pharma Sciences, LLC		
Appl No.:	16/248,460	Confirmation No.:	6641
Filed:	January 15, 2019	Group Art Unit:	1615
For:	STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE		

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

In response to the Notice to File Corrected Application Papers dated February 7, 2019, enclosed are the following:

- ☐ Part 2 of Formalities Letter (not necessary when e-filing)
- ☐ Declaration and Power of Attorney for the above-identified application, which has been executed by the named inventor(s)
- ☐ Declaration of Inventors which has been executed by the named inventor(s) and an Assignee Power of Attorney
- ☐ Applicant claims small entity status
- ☐ Check in the amount of to cover the filing fee of and the surcharge under 37 C.F.R.§ 1.16(f)
- ☐ All fees are being authorized to be charged to Deposit Account No. 16-0605 when electronically filing
- ☐ English Translation and $130.00 (37 CFR 1.17(i)) fee for filing late.
- ☒ Other: Statement Under 37 CFR 1.125(b) and Substitute Specification (Clean and mark-up)
- ☒ Any deficiency, additional fee, or credit may be charged to our Deposit Account No. 16-0605.

Respectfully submitted,

/Bryan L. Skelton/

Bryan L. Skelton
Registration No. 50,893

Customer No. 00826
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STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE

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.

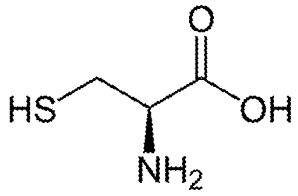
Additionally, controlling heat in the process including during the compounding and/or sterilization activities, unexpectedly was found to be beneficial for preparing stable L-Cysteine compositions described herein. This was surprising because L-Cysteine has been used in parenteral products as an excipient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

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
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

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~~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~~

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~~

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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~~

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 yrs to 17 yrs~~	~~10.66 to 20~~	~~0.007 to 0.012~~	~~0.017 to 0.029~~	~~0.04 to 0.07~~	~~0.05 to 0.088~~
~~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~~

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 yrs to 17 yrs	10.66 to 20	0.007 to 0.012	0.017 to 0.029	0.04 to 0.07	0.05 to 0.088
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) 16th 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. 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" 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 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 Head Space Gas Analysis	Dissolved Oxygen =Report Value 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 Head Space Gas Analysis	Dissolved Oxygen =Report Value 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~~

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**

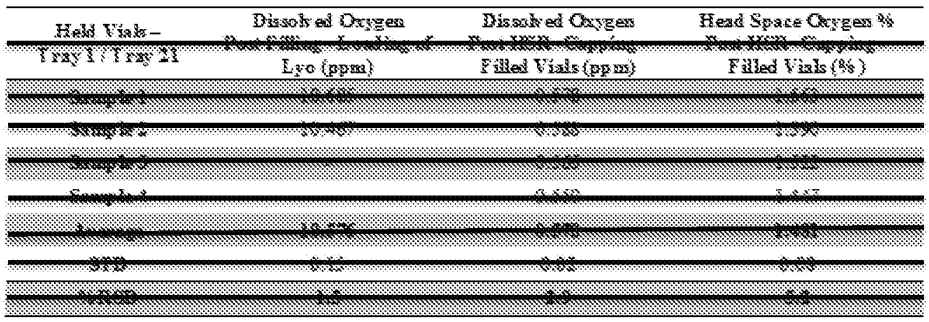
Table 11. Filled Vials Head Space Oxygen.

~~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~~

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

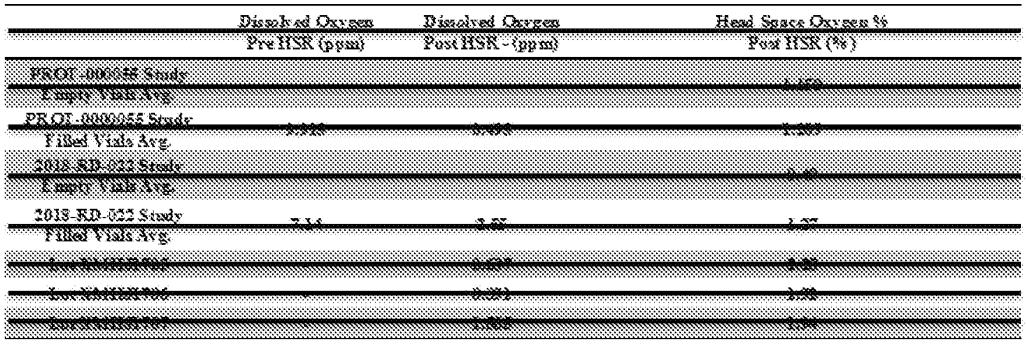
Table 12. Held vials dissolved oxygen (ppm) and head space oxygen content (%).



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	[illegible]	[illegible]	[illegible]
Sample 2	[illegible]	[illegible]	[illegible]
Sample 3	[illegible]	[illegible]	[illegible]
Sample 4	[illegible]	[illegible]	[illegible]
Average	[illegible]	[illegible]	[illegible]
STD	[illegible]	[illegible]	[illegible]
%RSD	[illegible]	[illegible]	[illegible]

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.	[illegible]	[illegible]	[illegible]
PROT-000055 Study Filled Vials Avg.	[illegible]	[illegible]	[illegible]
2018-RD-022 Study Empty Vials Avg.	[illegible]	[illegible]	[illegible]
2018-RD-022 Study Filled Vials Avg.	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

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	Dissolved Oxygen Pre HSR (ppm)	**Dissolved Oxygen Post HSR – (ppm)**	**Head Space Oxygen % Post HSR (%)**
PROT-000055 Study	-	-	**1.150**

Empty Vials Avg.			
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~~

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~~

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 Low High	2.3 % Oxygen N/A N/A	1.9 % Oxygen N/A N/A	1.9 % Oxygen N/A N/A	0.4 % Oxygen 0.2% Oxygen 0.5% Oxygen
1 Month Room Temperature	0.9 % Oxygen	2.8 % Oxygen	1.2 % Oxygen	1.1 % Oxygen (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~~

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: L-Cystine Pyruvic Acid Total Specified RRT-1.98 Individual Unspecified Total Impurities	 0.3% 0.1% 0.2% ND 0.5%	 0.3% 0.2% 0.2% ND 0.7%	 0.3% 0.1% 0.2% ND 0.6%
Dissolved Oxygen	(1) 0.12 ppm (2) 0.13 ppm	(1) 0.13 ppm (2) 0.14 ppm	(1) 0.14 ppm (2) 0.13 ppm
Head-Space Oxygen	(1) 0.16% (2) 0.37%	(1) 0.53% (2) 0.89%	(1) 0.56% (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

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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 °C/60 %RH**				**XMHJ1705 40 °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 °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 °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 °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.

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

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.

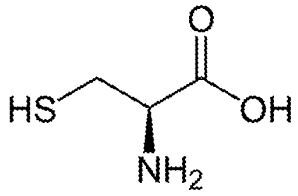
Additionally, controlling heat in the process including during the compounding and/or sterilization activities, unexpectedly was found to be beneficial for preparing stable L-Cysteine compositions described herein. This was surprising because L-Cysteine has been used in parenteral products as an excipient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

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
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

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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 yrs to 17 yrs	10.66 to 20	0.007 to 0.012	0.017 to 0.029	0.04 to 0.07	0.05 to 0.088
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 ℃ / 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) 16th 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. 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" 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 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 Head Space Gas Analysis	Dissolved Oxygen =Report Value 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 Head Space Gas Analysis	Dissolved Oxygen =Report Value 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**

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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 Low High	2.3 % Oxygen N/A N/A	1.9 % Oxygen N/A N/A	1.9 % Oxygen N/A N/A	0.4 % Oxygen 0.2% Oxygen 0.5% Oxygen
1 Month Room Temperature	0.9 % Oxygen	2.8 % Oxygen	1.2 % Oxygen	1.1 % Oxygen (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: L-Cystine Pyruvic Acid Total Specified RRT-1.98 Individual Unspecified Total Impurities	 0.3% 0.1% 0.2% ND 0.5%	 0.3% 0.2% 0.2% ND 0.7%	 0.3% 0.1% 0.2% ND 0.6%
Dissolved Oxygen	(1) 0.12 ppm (2) 0.13 ppm	(1) 0.13 ppm (2) 0.14 ppm	(1) 0.14 ppm (2) 0.13 ppm
Head-Space Oxygen	(1) 0.16% (2) 0.37%	(1) 0.53% (2) 0.89%	(1) 0.56% (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

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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 °C/60 %RH**				**XMHJ1705 40 °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 °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 °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 °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.

Attorney's Docket No. 066859/509450 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Exela Pharma Sciences, LLC		
Appl No.:	16/248,460	Confirmation No.:	6641
Filed:	January 15, 2019	Group Art Unit:	1615
For:	STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE		

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT UNDER 37 C.F.R. §1.125
REGARDING SUBSTITUTE SPECIFICATION

I hereby state that the Substitute Specification filed concurrently herewith is in compliance with 37 C.F.R. §1.125. In compliance with 37 C.F.R. §1.125(b), the substitute specification does not include the claims. The Substitute Specification corrects the purported deficiencies as set forth in the Notice to File Corrected Application Papers dated February 7, 2019, and contains no new matter. Enclosed is both a clean and a marked copy of the Substitute Specification in compliance with 37 C.F.R. §1.125(c). The Substitute Specification submitted herewith is believed to be fully compliant with 37 CFR §§ 1.52, 1.121(b)(3) and 1.125. Accordingly, this is a *bona fide* attempt to comply with the Notice.

It is not believed that 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 are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefor (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

/ Bryan L. Skelton /

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Electronic Acknowledgement Receipt

EFS ID:	35312163
Application Number:	16248460
International Application Number:	
Confirmation Number:	6641
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/Karen Trachtman
Filer Authorized By:	Bryan Lee Skelton
Attorney Docket Number:	066859/509450
Receipt Date:	04-MAR-2019
Filing Date:	15-JAN-2019
Time Stamp:	16:13:25
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	Applicant Response to Pre-Exam Formalities Notice	2019-03-04_Response_NTFCAP.pdf	64999 eb484f626942770e8a6e3a3f59e2f63a15060020	no	1

Warnings:

Information:					
2	Specification	2019-03-04_Substitute_Specification-MARKED.pdf	795305 81fe1c777b7dddf795f201a3aa4e32711d9cf360	no	91
Warnings:					
Information:					
3	Specification	2019-03-04_Substitute_Specification-CLEAN.pdf	578475 889c5001948a58605b5033b0050ad61359c5cf33	no	86
Warnings:					
Information:					
4	Applicant Response to Pre-Exam Formalities Notice	2019-03-04_Stmt_37CFR1_125_re_Substitute_Specification.pdf	73611 ea88fbca4a8a4012b6e7cfe611483bbda0f057cc	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1512390		

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.
<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.
<u>New International Application Filed with the USPTO as a Receiving Office</u>
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.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/248,460

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	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	22 minus 20 =	* 2			OR	x 100 =	200
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x 460 =	0.00
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).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1920

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($)	ADDITIONAL FEE($)	OR	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 NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/248,460	01/15/2019	1615	2080	066859/509450	22	3

CONFIRMATION NO. 6641

UPDATED FILING RECEIPT

826
ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

OC000000106383780

Date Mailed: 03/07/2019

Receipt is acknowledged of this non-provisional 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 APPLICANT, 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 Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections 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**

Inventor(s)

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

Applicant(s)

Exela Pharma Sciences, LLC, Lenoir, NC

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

Domestic Applications for which benefit is claimed - None.
A proper domestic benefit claim must be provided in an Application Data Sheet in order to constitute a claim for domestic benefit. See 37 CFR 1.76 and 1.78.

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: 02/06/2019

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/248,460**

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

424

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

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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.

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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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/248,460	01/15/2019	John Maloney	066859/509450	6641

826 7590 03/15/2019

ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER	
ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
03/15/2019	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.** 16/248,460	**Applicant(s)** Maloney et al.	
	Examiner CHERYL P GIBSON BAYLOR	**Art Unit** OPET	**AIA (First Inventor to File) Status** Yes

1. THE REQUEST FILED 15 January 2019 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 CHERYL GIBSON BAYLOR at (571)272-3213. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/CHERYL GIBSON BAYLOR/ Paralegal Specialist, OPET	

Substitute for form 1449B/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/248,460
				Filing Date	January 15, 2019
				First Named Inventor	John Maloney
				Art Unit	1612
(Use as many sheets as necessary)				Examiner Name	Benjamin J. Packard
Sheet	1	of	14	Attorney Docket Number	066859/509450

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number / 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
	209	US 6,992,218 B2	01-31-2006	Dietlin et al.	
	001	US 7,323,206 B1	01-29-2008	Driscoll et al.	
	002	US 9,220,700 B2	12-29-2015	Savarese et al.	

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]
	003	"Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients," ASPEN Board of Directors and the Clinical Guidelines Task Force, Journal of Parenteral and Enteral Nutrition, 26(1 Suppl.):1SA-138SA, (2002).	
	004	"ACETADOTE (acetylcysteine) injection, for intravenous use: Prescribing Information [package insert]," Cumberland Pharmaceuticals Inc., 12 pages, (2017).	
	005	"AMINOSYN [prescribing information and label]," Hospira, Inc., 19 pages, (2012).	
	006	"ASHP Guidelines on the Safe Use of Automated Compounding Devices for the Preparation of Parenteral Nutrition Admixtures," Automation and Information Technology–Guidelines, 63–67, (2000).	
	007	"Chapter 18: Preparation of Parenteral Nutrition," Aseptic Processing Manual, NHS Technical Specialist Education and Training Group, 24 pages, (2018).	
	008	"Cysteine Hydrochloride Injection [Material Safety Data Sheet]," Hospira Inc., 6 pages, (2011).	
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Examiner Signature		Date Considered	

Substitute for form 1449B/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/248,460
				Filing Date	January 15, 2019
				First Named Inventor	John Maloney
				Art Unit	1612
(Use as many sheets as necessary)				Examiner Name	Benjamin J. Packard
Sheet	2	of	14	Attorney Docket Number	066859/509450

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Examiner Signature		Date Considered	

Substitute for form 1449B/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/248,460
				Filing Date	January 15, 2019
				First Named Inventor	John Maloney
				Art Unit	1612
(Use as many sheets as necessary)				Examiner Name	Benjamin J. Packard
Sheet	3	of	14	Attorney Docket Number	066859/509450

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Examiner Signature		Date Considered	

Substitute for form 1449B/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/248,460
				Filing Date	January 15, 2019
				First Named Inventor	John Maloney
				Art Unit	1612
(Use as many sheets as necessary)				Examiner Name	Benjamin J. Packard
Sheet	4	of	14	Attorney Docket Number	066859/509450

	047	CARLSON et al., "Neonatal Parenteral and Enteral Nutrition: A Resource Guide for the Student and Novice Neonatal Nurse Practitioner," National Association of Neonatal Nurse Practitioners, 23 pages, (2010).	
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Examiner Signature		Date Considered	

Substitute for form 1449B/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/248,460
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(Use as many sheets as necessary)				Examiner Name	Benjamin J. Packard
Sheet	5	of	14	Attorney Docket Number	066859/509450

	062	FEWTRELL et al., "Aluminium exposure from parenteral nutrition in preterm infants and later health outcomes during childhood and adolescence," Symposium 2: Micronutirents under the Microscope, Proceedings of the Nutrition Society, 70(3):299-304, (2011). [Retrieved from the Internet June 4, 2018: <URL: https://www.cambridge.org/core/journals/proceedings-of-the-nutrition-society/article/aluminium-exposure-from-parenteral-nutrition-in-preterm-infants-and-later-health-outcomes-during-childhood-and-adolescence/F5D0A6109616E8C9D7F8C2C707213860/core-reader>].	
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Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/248,460
				Filing Date	January 15, 2019
				First Named Inventor	John Maloney
				Art Unit	1612
(Use as many sheets as necessary)				Examiner Name	Benjamin J. Packard
Sheet	13	of	14	Attorney Docket Number	066859/509450

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Examiner Signature		Date Considered	

Substitute for form 1449B/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/248,460
				Filing Date	January 15, 2019
				First Named Inventor	John Maloney
				Art Unit	1612
(Use as many sheets as necessary)				Examiner Name	Benjamin J. Packard
Sheet	14	of	14	Attorney Docket Number	066859/509450

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Examiner Signature		Date Considered	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Exela Pharma Sciences, LLC	Confirmation No.:	6641
Appl. No.:	16/248,460	Group Art Unit:	1612
Filed:	January 15, 2019	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 along with a copy of all listed documents (other than U.S. patents, U.S. patent application publications, or patents or publications otherwise determined cumulative) in accordance with 37 CFR 1.98(a)(2).

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.

Respectfully submitted,

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Electronic Acknowledgement Receipt

EFS ID:	35964085
Application Number:	16248460
International Application Number:	
Confirmation Number:	6641
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/Laura Tremont
Filer Authorized By:	Bryan Lee Skelton
Attorney Docket Number:	066859/509450
Receipt Date:	10-MAY-2019
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Time Stamp:	10:49:31
Application Type:	Utility under 35 USC 111(a)

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Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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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.

Electronic Acknowledgement Receipt

EFS ID:	35966115
Application Number:	16248460
International Application Number:	
Confirmation Number:	6641
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/Laura Tremont
Filer Authorized By:	Bryan Lee Skelton
Attorney Docket Number:	066859/509450
Receipt Date:	10-MAY-2019
Filing Date:	15-JAN-2019
Time Stamp:	10:51:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

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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.

Electronic Acknowledgement Receipt

EFS ID:	35966809
Application Number:	16248460
International Application Number:	
Confirmation Number:	6641
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/Laura Tremont
Filer Authorized By:	Bryan Lee Skelton
Attorney Docket Number:	066859/509450
Receipt Date:	10-MAY-2019
Filing Date:	15-JAN-2019
Time Stamp:	10:53:23
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

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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.

Electronic Acknowledgement Receipt

EFS ID:	35966973
Application Number:	16248460
International Application Number:	
Confirmation Number:	6641
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/Laura Tremont
Filer Authorized By:	Bryan Lee Skelton
Attorney Docket Number:	066859/509450
Receipt Date:	10-MAY-2019
Filing Date:	15-JAN-2019
Time Stamp:	10:54:49
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

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17	Non Patent Literature	197-Wlodek_1988.pdf	1972573 314c4241c5363955e8ee2154297c8daa3ff0890f	no	11
Warnings:					
Information:					
18	Non Patent Literature	198-Woolsey_2008.PDF	205965 73198819f98b842827889b96c3b4f80db662e8d4	no	6
Warnings:					
Information:					
19	Non Patent Literature	199-Yamaguchi_1973.pdf	1678760 d0a1b0162de680071c2dd8b857291ad4597bf757	no	12
Warnings:					
Information:					
20	Non Patent Literature	200-Yao_1997.pdf	1417674 073f551249363c8b6dc8161706a1a461e6b333f2	no	10
Warnings:					
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21	Non Patent Literature	201-Yao_perfusedratliver_1997.pdf	1165863 7e402cebbafa4f6287a06d3a3d94da3f411bcf12	no	8
Warnings:					
Information:					
22	Non Patent Literature	202-Yarandi_2011.pdf	175892 ae8fd93dee02f73bf5edae244d1efeade1e5 3244	no	14
Warnings:					
Information:					

23	Non Patent Literature	203-Ybarra_2010.pdf	378485 5d223d2edbc40704b62b48ddfe19768eefef703c	no	4
Warnings:					
Information:					
24	Non Patent Literature	204-Yin_2015.PDF	774708 f480cd1e712dd75497e426b63525a99a6edf8e19	no	13
Warnings:					
Information:					
25	Non Patent Literature	205-Zerangue_1996.pdf	2962123 e2e7d59fccffb57862e9bab665bf8d1601bd6ae7	no	5
Warnings:					
Information:					
26	Non Patent Literature	206-Zhang_2009.pdf	1733117 c1a38f1545eb0e2c9795a5cc9e41f208c435e616	no	33
Warnings:					
Information:					
27	Non Patent Literature	207-Zlotkin_1981.pdf	4965968 00f99f0b47c2e40d550015d89b0d8885da8c3bf5	no	10
Warnings:					
Information:					
28	Non Patent Literature	208-Zlotkin_1982.pdf	348432 4ac1ff64b7547c0fa6e6596efb18325e3afe02a6	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	39596751		

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 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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/248,460	01/15/2019	John Maloney	066859/509450	6641

826 7590 06/19/2019

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CHARLOTTE, NC 28280-4000

EXAMINER	
PACKARD, BENJAMIN J	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
06/19/2019	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.** 16/248,460	**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) 1-22 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) 1-22 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 14pgs (55/10/19).

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.

Claim Rejections - 35 USC § 112 - Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a

reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to chemical synthesis and purification. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

art. As illustrative of the state of the art, the examiner cites Lima-Rogel et al ((2016), Aluminum Contamination in Parenteral Nutrition Admixtures for Low-Birth-Weight Preterm Infants in Mexico. Journal of Parenteral and Enteral Nutrition, 40: 1014-1020) and Hintz, et al ((2008), Aluminum Exposure From Pediatric Parenteral Nutrition: Meeting the New FDA Regulation. JPEN J Parenter Enteral Nutr, 32: 242-246) which disclose while aluminum contamination is a known problem, it is unknown how to reduce the aluminum content of formulations.

2. The breadth of the claims

The claims are broadly drawn to a composition having claimed properties, but with no disclosure or limitations as to how those properties are achieved.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for practicing the claimed invention in its "full scope". No reasonably specific guidance is provided concerning useful protocols for carrying out the invention as claimed, other than the prophetic process at pg 51, which does not provide an explanation or evidence that the contamination content will be lower than already commonly present. The latter is corroborated by the working examples.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used as inferred by the claim and contemplated by the specification. Accordingly, the instant

claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no reasonable expectation of success. Specifically, the only disclosure appears to be mixing L-cysteine with minimum contaminates (see ex claim 22) but there is no disclosure how the compound is made pure or avoid impurities known in the art. Instant claim 21 suggests using reduced head space oxygen, but it is unclear how that will reduce contaminates already present.

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

While it is unclear how the invention is enabled as discussed above, it appears the two clear limitations are L-cysteine and low oxygen head space. As such, the following rejection is made of record to further prosection.

Claims 1-13 and 15-22 is/are rejected under 35 U.S.C. 103 as being unpatentable over Sigma-Aldrich product information, L-cysteine hydrochloride mononyhdrate (05/06) in view of Whiting et al (Journal of Food Protection, Vol. 55, No. 1, Pages 23-27, January 1992).

Sigma-Aldrich discloses L-cysteine is soluble in water at 100 mg/ml.

Whiting et al discloses it was known that oxygen in the headspace can allow outgrowth and toxin production.

It would have been obvious to one of ordinary skill in the art to store the solution of Sigma-Aldrich in an oxygen reduced atmosphere to reduce the chances of undesired reactions causing side products.

While the references do not disclose the impurity content, given the disclosure is for the compound per se, it is reasonably expected that the impurity content is below the claimed amount where the disclosures above suggest the impurities come from combination products.

With regards to the steps of claim 21, where the end result is reduced oxygen exposure, it would have been obvious to use an alternate gas when mixing to reduce the oxygen absorption during formulation.

Claims 1 and 14 is/are rejected under 35 U.S.C. 103 as being unpatentable over Jalilehvand et al (Inorg. Chem., 2015, 54 (5), pp 2160–2170).

Jalilehvand et al discloses lead in aqueous solution with L-cysteine (abstract).

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 on 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 an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BENJAMIN J PACKARD/
Primary Examiner, Art Unit 1612

Notice of References Cited	Application/Control No. 16/248,460	Applicant(s)/Patent Under Reexamination Maloney et al.	
	Examiner BENJAMIN J PACKARD	Art Unit 1612	Page 1 of 2

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Jalilehvand et al (Inorg. Chem., 2015, 54 (5), pp 2160–2170). (Year: 2015)
	V	Sigma-Aldrich product information, L-cysteine hydrochloride mononyhdrate (05/06). (Year: 2006)
	W	Whiting et al (Journal of Food Protection, Vol. 55, No. 1, Pages 23-27, January 1992). (Year: 1992)
	X	Lima-Rogel et al ((2016), Aluminum Contamination in Parenteral Nutrition Admixtures for Low-Birth-Weight Preterm Infants in Mexico. Journal of Parenteral and Enteral Nutrition, 40: 1014-1020) (Year: 2016)

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 16/248,460	Applicant(s)/Patent Under Reexamination Maloney et al.	
	Examiner BENJAMIN J PACKARD	Art Unit 1612	Page 2 of 2

U.S. PATENT DOCUMENTS

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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Hintz, et al ((2008), Aluminum Exposure From Pediatric Parenteral Nutrition: Meeting the New FDA Regulation. JPEN J Parenter Enteral Nutr, 32: 242-246). (Year: 2008)
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/248,460	Maloney et al.
	Examiner	Art Unit
	BENJAMIN J PACKARD	1612

CPC - Searched*		
Symbol	Date	Examiner

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 inventor search	05/13/2019	BP
East search	05/13/2019	BP
CAPlus search- L-cysteine, impurities, aluminum, lead	05/13/2019	BP

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

Substitute for form 1449B/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/248,460
				Filing Date	January 15, 2019
				First Named Inventor	John Maloney
				Art Unit	1612
(Use as many sheets as necessary)				Examiner Name	Benjamin J. Packard
Sheet	1	of	14	Attorney Docket Number	066859/509450

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number / 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
	209	US 6,992,218 B2	01-31-2006	Dietlin et al.	
	001	US 7,323,206 B1	01-29-2008	Driscoll et al.	
	002	US 9,220,700 B2	12-29-2015	Savarese et al.	

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]
	003	"Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients," ASPEN Board of Directors and the Clinical Guidelines Task Force, Journal of Parenteral and Enteral Nutrition, 26(1 Suppl.):1SA-138SA, (2002).	
	004	"ACETADOTE (acetylcysteine) injection, for intravenous use: Prescribing Information [package insert]," Cumberland Pharmaceuticals Inc., 12 pages, (2017).	
	005	"AMINOSYN [prescribing information and label]," Hospira, Inc., 19 pages, (2012).	
	006	"ASHP Guidelines on the Safe Use of Automated Compounding Devices for the Preparation of Parenteral Nutrition Admixtures," Automation and Information Technology–Guidelines, 63–67, (2000).	
	007	"Chapter 18: Preparation of Parenteral Nutrition," Aseptic Processing Manual, NHS Technical Specialist Education and Training Group, 24 pages, (2018).	
	008	"Cysteine Hydrochloride Injection [Material Safety Data Sheet]," Hospira Inc., 6 pages, (2011).	
	009	"Cysteine Hydrochloride Injection [prescribing information]," Hospira, Inc., 4 pages, (2004). [Retrieved from the Internet December 28, 2016: <URL: https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=113819>].	
	010	"Cysteine," TOXNET: Toxicology Data Network, National Library of Medicine HSDB Database, 20 pages, (2016). [Retrieved from the Internet June 27, 2017: <URL: https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+2109>].	
	011	"Cysteine: Pediatric drug information," Lexicomp, Inc., 4 pages, (1978).	
	012	"Determination That Cysteine Hydrochloride Injection, USP, 7.25%, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness," Federal Register, 75(107):31790-31791, (2010).	
	013	"Effect of L-Cysteine (Acetium® Capsules) in Restoration of the Structure and Function of Gastric Mucosa After H. pylori Eradication in Patients with Atrophic Gastritis. A randomized, controlled trial.," Study Protocol, BIOHIT HealthCare, 45 pages, (2016).	
	014	"Guideline on the Use of Parenteral Nutrition in Neonatal and Paediatric Units," Clinical Practice Guideline, Royal College of Physicians in Ireland, 46 pages, (2016).	

Examiner Signature	/BENJAMIN J PACKARD/	Date Considered	05/13/2019

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	16/248,460
				Filing Date	January 15, 2019
				First Named Inventor	John Maloney
				Art Unit	1612
(Use as many sheets as necessary)				Examiner Name	Benjamin J. Packard
Sheet	2	of	14	Attorney Docket Number	066859/509450

	015	"L-Cysteine [product information]," Sigma-Aldrich, Inc., 2 pages, (2003).	
	016	"L-CYSTEINE HYDROCHLORIDE [prescribing information and label]", Sandoz Inc., 6 pages, (2010).	
	017	"L-Cysteine Hydrochloride Injection, USP [prescribing information]," American Regent, Inc., 2 pages, (2009).	
	018	"PROSOL [prescribing information and label]," Baxter Healthcare Corporation, 14 pages, (2014).	
	019	"Safe Practices for Parenteral Nutrition Formulations," National Advisory Group on Standards and Practice Guidelines for Parenteral Nutrition, Journal of Parenteral and Enteral Nutrition, 22(2):49-66, (1998). [Retrieved from the Internet March 12, 2015: <URL: https://onlinelibrary.wiley.com/doi/10.1177/014860719802200249>].	
	020	"Scientific Opinion on the safety and efficacy of L-cysteine hydrochloride monohydrate as a flavouring additive for pets," European Food Safety Authority Journal, 11(10):3437, 13 pages, (2013).	
	021	"The Provision of Parenteral Nutrition within Neonatal Services - A Framework for Practice," British Association of Perinatal Medicine, 27 pages, (2016).	
	022	"TRAVASOL [prescribing information and label]," Baxter Healthcare Corporation, 19 pages, (2017).	
	023	"TROPHAMINE [prescribing information and label]," B. Braun Medical Inc., 21 pages, (2014).	
	024	"TROPHAMINE® (Amino Acid Injections) [package insert]," B. Braun Medical Inc., pp. 5-16, (2003).	
	025	ABDULRAZIK et al., "Formulation for Slow Release of Oral Radiation-Protection Drugs," Int. J. Nucl. Med. Biol., 11(1):53-54, (1984).	
	026	ADVENIER et al., "Aluminum Contamination of Parenteral Nutrition and Aluminum Loading in Children on Long-Term Parenteral Nutrition," Journal of Pediatric Gastroenterology and Nutrition, 36(4):448-453, (2003). [Retrieved from the Internet June 6, 2018: <URL: https://journals.lww.com/jpgn/Fulltext/2003/04000/Aluminum_Contamination_of_Parenteral_Nutrition_and.5.aspx#pdf-link>].	
	027	ALLEN, Jr., Loyd V., "L-Cysteine Hydrochloride 50 mg/mL Injection," U.S. Pharmacist, 36(9):41-42, (2011). [Retrieved from the Internet May 26, 2016: <URL:https://www.uspharmacist.com/article/lcysteinehydrochloride50mgmlinjection>].	
	028	ALLEN, Loyd V., "Chapter 1: Guidelines for Compounding Practices," The Art, Science, and Technology of Pharmaceutical Compounding, 4th Ed.:1-18, (2012).	
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				Filing Date	January 15, 2019
				First Named Inventor	John Maloney
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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	563	"l-cysteine" aluminum "pyruvic acid"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2019/05/13 20:28
L3	4	"l-cysteine".clm. aluminum cystine pyruvic acid	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2019/05/13 20:29
S2	98	"l-cysteine" aluminum cystine pyruvic acid	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2019/05/13 16:16
S3	129	"l-cysteine" aluminum contaminate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2019/05/13 16:53
S4	38	"l-cysteine" aluminum contaminate parenteral	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2019/05/13 16:53

5/ 13/ 2019 8:30:55 PM
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.:	16/248,460	Confirmation No.: 6641
Applicant(s):	Exela Pharma Sciences, LLC	
Filed:	January 15, 2019	
Art Unit:	1612	
Examiner:	Packard, Benjamin J.	
Title:	STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE	

Docket No.: 066859/509450
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 June 19, 2019 ("Office Action"), Applicant respectfully submits:

A **Listing of the Claims** beginning on page 2 of this paper; and

Remarks beginning on page 7 of this paper.

Listing of the Claims:

1. (Original) 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 oxygen that is from about 0.5% v/v to 4.0% v/v 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. (Original) The composition of claim 1, wherein the composition is essentially free of an antioxidant.

3. (Original) The composition of claim 1, wherein said Aluminum is present in an amount from about 1.0 ppb to about 200 ppb.

4. (Original) The composition of claim 1, wherein said Aluminum is present in an amount from about 1.0 ppb to about 150 ppb.

5. (Original) The composition of claim 1, wherein said Aluminum is present in an amount from about 1.0 ppb to about 100 ppb.

6. (Original) The composition of claim 1, wherein said Aluminum is present in an amount from about 1.0 ppb to about 50 ppb.

7. (Original) The composition of claim 1, wherein said Aluminum is present in an amount from about 1.0 ppb to about 20 ppb.

8. (Original) The composition of claim 1, wherein the composition 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, wherein the total amount of Aluminum is from about 4.0 ppb to about 250 ppb.

9. (Original) The composition of claim 1, wherein said L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof is present in an amount from about 20 mg/mL to about 70 mg/mL.

10. (Original) The composition of claim 1, wherein said L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof is present in an amount from about 30 mg/mL to about 70 mg/mL.

11. (Original) The composition of claim 1, wherein said L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof is present in an amount of about 37.5 mg/mL.

12. (Original) The composition of claim 1, wherein said headspace oxygen is from about 2.0% v/v to about 4.0% v/v.

13. (Original) The composition of claim 1, wherein said headspace oxygen is from about 3.0% v/v to about 4.0% v/v.

14. (Original) The composition of claim 1, further comprising one or more heavy metals selected from the group consisting of Lead, Nickel, Arsenic and Mercury.

15. (Original) A total parenteral nutrition composition for parenteral administration, comprising an admixture of:

about 0.5 mL to about 10 mL an L-cysteine composition 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 10 ppb to about 80 ppb;

L-cystine in an amount from about 0.0.1 wt% to about 2.0 wt% relative to L-cysteine;

pyruvic acid in an amount from about 0.0.1 wt% to about 2.0 wt% relative to L-cysteine;

a pharmaceutically acceptable carrier, comprising water;

headspace oxygen that is from about 0.5% v/v to 4.0% v/v 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,

and, about 1 gram to 200 grams of an amino acid 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.

16. (Original) The composition of claim 15, where said L-cysteine composition and said amino acid composition are present in the admixture at a ratio of from about 1:50 to 1:1000.

17. (Original) The composition of claim 15, 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;

From about 10 mg/g amino acid to about 80 mg/g of 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

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

18. (Original) The composition of claim 17, wherein said L-cysteine is present at about 30 mg/g to about 50 mg/g of total amino acid content.

19. (Original) The composition of claim 17, wherein said L-cysteine is present at about 40 mg/g of total amino acid content.

20. (Original) The composition of claim 15, having a volume of about 100 mL to about 1000 mL for infusion within about 24 hours to about 48 hours of admixture.

21. (Currently amended) A method of preparing the composition of claim 1, 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]] 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 mixture into containers of use;

Reducing head space oxygen in said containers of use; and

Sealing said containers of use, wherein the dissolved oxygen in said containers of use is about 0.1 ppm to about 5 ppm.

22. (Original) A method of preparing a reduced Aluminum composition for 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.

REMARKS/ARGUMENTS

Upon entry of the foregoing amendments, Claims 1-22 are pending and under examination in this application.

Claim 21 is being amended to correct a minor clerical error where two letters were inadvertently transposed. The term "NTL" has been replaced with the term "NLT," which is a term of art used as an abbreviation for "not less than." No new matter is being added by this amendment. Applicant respectfully requests its entry.

Based on the following remarks, Applicant submits that all of the claims are in condition for allowance. Accordingly, Applicant respectfully requests favorable reconsideration and issuance of a Notice of Allowance.

I. Statement of the Substance of the Interview

A web-based interview was conducted on August 28, 2019, in which Examiner Benjamin Packard, co-inventors Drs. Phanesh Koneru, John Maloney and Aruna Koganti, and Applicant's undersigned attorney Bryan Skelton participated. Applicant sincerely thanks Examiner Packard for taking time to discuss the issues. During the interview, the rejections set forth in the Office Action dated June 19, 2019, and the pending claims were discussed. Applicant explained some of the unexpected technical hurdles that it had to overcome, including the reduction of Aluminum levels, and having reached acceptable Aluminum levels, the identification of the problems of oxygen-susceptibility and stability. Applicant described the support for the claims as provided in the present specification, including the Examples. Examiner Packard and Applicant discussed the cited art and its reporting of the problem of Aluminum levels in known L-cysteine products. Examiner Packard and Applicant discussed potential allowability of the subject matter of the present claims after Applicant herein files its formal response to the Office Action.

II. Response to Rejections Under § 112(a)

Claims 1-22 stand rejected for allegedly failing to comply with the enablement requirement. *Office Action, page 2.* In the Office Action, several *Wands* factors are discussed. *Office Action, beginning at page 3.* Applicant respectfully traverses the rejection for the following reasons.

The Office Action cites several art references and avers that while "aluminum contamination is a known problem, it is unknown how to reduce the aluminum content of the

formulations." *Id. at page 4.* In this aspect, during the interview, Applicant discussed with Examiner Packard that the cited art reports on the problem at hand, which after many years was still unsolved prior to the present inventors' solution as described in the present application. However, turning to the text throughout the present specification, it sets forth that the present inventors addressed many variables and describes the factors that the present inventors used to overcome the Aluminum safety issues at hand, for example: "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 . . . ." *Present Specification, page 6, lines 25-28.*

The Office Action alleges that there is no disclosure or guidance to arrive at the claimed compositions. See, *Office Action, pages 4-5, Items, 2, 3 and 4.* The Office Action alleges that there is only "the prophetic process at pg 51, which does not provide an explanation or evidence that the contamination content will be lower than already commonly present." *Office Action, page 4.* The Office Action alleges that experimental evidence is absent. *Id., at page 4.*

Turning again to the present specification, the variables to be addressed and the factors used are described, *inter alia*, in the Examples beginning on page 61. Here, it is described to the person of ordinary skill how to make the claimed compositions as well as how unexpected technical issues and product failures were overcome. The Examples disclose at the very least: how to compound and fill representative L-cysteine compositions (Example 1, page 61); how lack of control for Aluminum leaching ultimately results in Aluminum levels that while lower than known products, are still deemed unacceptably high (levels that are outside the scope of the present claims)(Example 2, page 62); how plastic vials while achieving exceedingly low Aluminum levels unexpectedly result in unacceptable precipitate formation within one month (Example 3, pages 62-63); and how to accomplish head space oxygen reduction using a lyophilizer (Example 4, pages 63-68) or automated filling equipment (Example 5, pages 69-72). Further, in Example 6, the present specification provides additional experimental evidence in Table 18 on page 72, in the form of test data for purity and long-term stability of three batches compounded and filled by the processes taught in the present specification. The data in Table 18 and the Figures show that controlling for Aluminum and oxygen by the processes described in the present specification result in the lowest impurity profile obtained for the claimed compositions.

Having set forth how to make the claimed compositions through processes described in the present specification, Applicant has met the burden for enablement—whether any experimentation needed to practice the invention would be undue or unreasonable. *In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988); M.P.E.P. § 2164.01. In the present case, Applicant has done more than is required by actually performing the described processes and providing data, *inter alia*, in the Examples and Figures evincing the reduction to practice of the resulting compositions. As such, all of the present claims are enabled. Accordingly, Applicant respectfully requests withdrawal of the rejection.

III. Response to Rejections Under § 103(a)

i. Claims 1-13 and 15-22

Claims 1-13 and 15-22 stand rejected as allegedly being obvious over "Sigma-Aldrich product information" in view of Whiting, et al., *Journal of Food Protection*, 55, 1, pp. 23-27 (January 1992). *Office Action, page 6.* Applicant respectfully traverses the rejection for the following reasons.

The Office Action acknowledges that "the references do not disclose the impurity content . . ." and avers that "it is reasonably expected that the impurity content is below the claimed amount where the disclosures above suggest the impurities come from the combination products." *Office Action, page 6.* At the outset, Applicant respectfully disagrees that combining L-cysteine reagent grade as disclosed in Sigma-Aldrich product information with the teachings of Whiting, which discloses the effects of oxygen on formation of *Clostridium botulinum* toxin in a soy broth, would suggest (or even implicitly disclose) a reasonably reliable or reproducible impurity content, let alone, each element of the present claims. Moreover, there is no evidence that prior to the present application, the person of ordinary skill would have looked at the Office Action's combination of references to achieve the claimed invention described, let alone, with a reasonable expectation of success. As discussed above in Section II, and for brevity not repeated entirely here, it was only after the present inventors addressed and overcame the problem of Aluminum that they were confronted with the problems of stability and precipitate formation. Put another way, the art did not know about the additional problems. As set forth in the present specification, the present inventors addressed and overcame those problems as well to arrive at the presently claimed subject matter.

For at least this reason a *prima facie* case of obviousness has not been established. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection.

ii. Claims 1 and 14

Claims 1 and 14 stand rejected as allegedly being obvious over Jalilehvand, et al., *Inorg. Chem.*, 54, 5, pp. 2160-2170 (2015). *Office Action, page 6.* Applicant respectfully traverses the rejection for the following reasons.

The Office Action states that "Jalilehvand et al discloses lead in aqueous solution with L-cysteine." *Office Action, page 6.* Applicant respectfully points out that according to MPEP § 2143.03: "All claim limitations must be considered in judging the patentability of that claim against the prior art." (citing *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970)). No evidence has been provided that the composition of Jalilehvand et al describes or suggests the pharmaceutically acceptable L-cysteine compositions presently claimed.

For at least this reason a *prima facie* case of obviousness has not been established. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection.

CONCLUSION

For all the reasons above, each of the presently pending claims is in condition for allowance. Applicant respectfully requests favorable reconsideration. Should there be any issue that impedes allowance of a claim, the Examiner is invited to telephone the undersigned attorney so that the issue can be expeditiously resolved.

It is not believed that 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 are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefor (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

/bryan l. skelton/

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Electronic Acknowledgement Receipt

EFS ID:	37085106
Application Number:	16248460
International Application Number:	
Confirmation Number:	6641
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/Karen Trachtman
Filer Authorized By:	Bryan Lee Skelton
Attorney Docket Number:	066859/509450
Receipt Date:	06-SEP-2019
Filing Date:	15-JAN-2019
Time Stamp:	11:12:27
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		2019-09-06_509450_NF_OAR.pdf	174123 67ab80cda0324d49036a24d739efdcfaf699e6d6	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	6
	Applicant Arguments/Remarks Made in an Amendment	7	11
Warnings:			
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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.
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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/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/248,460	Filing Date 01/15/2019	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ 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).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	09/06/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 22	Minus	** 22	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/APRIL L. WALKER/
*** 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 number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. 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 12 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, 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.**

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NOTICE OF ALLOWANCE AND FEE(S) DUE

826 7590 10/03/2019

ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER
PACKARD, BENJAMIN J

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 10/03/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/248,460	01/15/2019	John Maloney	066859/509450	6641

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	$1000	$0.00	$0.00	$1000	01/03/2020

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.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

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)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

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 and an extra copy of the form should be submitted. 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.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

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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
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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.

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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.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/248,460	01/15/2019	John Maloney	066859/509450	6641

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	$1000	$0.00	$0.00	$1000	01/03/2020

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/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 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_____
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. _____

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16/248,460	01/15/2019	John Maloney	066859/509450	6641

826 7590 10/03/2019

ALSTON & BIRD LLP
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101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER	
PACKARD, BENJAMIN J	
ART UNIT	**PAPER NUMBER**
1612	

DATE MAILED: 10/03/2019

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.

PTOL-85 (Rev. 02/11)

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.

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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. 16/248,460	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 response filed 9/6/19.
   ☐ 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 1-22 . 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 _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. 1pg (attached).
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/BENJAMIN J PACKARD/
Primary Examiner, Art Unit 1612

Reasons for Allowance

The following is an examiner's statement of reasons for allowance:

As noted by Applicants, while compositions with L-cysteine have been known in the art, the contaminant of aluminum hinders the further use of the product, especially for certain patient populations where the contaminant is beyond what is allowable for FDA approval. As such, Applicants have used multiple means disclosed in the specification and in the claims to achieve a composition which is far below the FDA demand, filling an unmet need which has been present for quite a number of years. Because each step taken independently did not demonstrate the desired result and there was no obvious reason to combine the steps actually taken, the product as claimed cannot be viewed as obvious. Instead the unexpected result is due to the Applicants unexpected findings resulting from testing combinations of theories with no expectation of success.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

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 on 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 an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BENJAMIN J PACKARD/
Primary Examiner, Art Unit 1612

Applicant-Initiated Interview Summary	**Application No.** 16/248,460	**Applicant(s)** Maloney et al.	
	Examiner BENJAMIN J PACKARD	**Art Unit** 1612	**AIA (FITF) Status** Yes

All participants (applicant, applicants representative, PTO personnel):

(1) BENJAMIN J. PACKARD.

(2) Bryan Skelton.

(3) John Maloney.

(4) Aruna Koganti and Phanesh Konery.

Date of Interview: 28 August 2019.

Type: ☐ Telephonic ☑ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☑ Yes ☐ No.
If Yes, brief description: Showed slides of the development process.

Issues Discussed ☐101 ☐112 ☐102 ☑103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 1-22.

Identification of prior art discussed: art of record.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

We discussed the criticality of the aluminum impurity and what was required to lower the amount to the claimed range. We also discussed which steps were expected to reduce the contaminate, yet didn't, leading to unpredicatbility in the art..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/BENJAMIN J PACKARD/ Primary Examiner, Art Unit 1612	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/248,460	Maloney et al.
	Examiner	**Art Unit**
	BENJAMIN J PACKARD	1612

✓	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								
Final	Original	09/28/2019								
	1	=								
	2	=								
	3	=								
	4	=								
	5	=								
	6	=								
	7	=								
	8	=								
	9	=								
	10	=								
	11	=								
	12	=								
	13	=								
	14	=								
	15	=								
	16	=								
	17	=								
	18	=								
	19	=								
	20	=								
	21	=								
	22	=								

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/248,460	Maloney et al.
	Examiner	Art Unit
	BENJAMIN J PACKARD	1612

CPC						
Symbol					Type	Version
A61K	/	33	/	06	F	2013-01-01
A61K	/	31	/	191	I	2013-01-01
A61K	/	47	/	02	I	2013-01-01
A61K	/	33	/	36	I	2013-01-01
A61K	/	33	/	241	I	2019-01-01
A61K	/	33	/	28	I	2013-01-01
A61K	/	33	/	00	I	2013-01-01
A61K	/	31	/	405	I	2013-01-01
A61K	/	31	/	401	I	2013-01-01
A61K	/	31	/	4172	I	2013-01-01
A61K	/	9	/	0029	I	2013-01-01
A23L	/	33	/	175	I	2016-08-01
A23L	/	33	/	16	I	2016-08-01
A61K	/	31	/	198	I	2013-01-01
A61K	/	31	/	095	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)	22	
/BENJAMIN J PACKARD/ Primary Examiner, Art Unit 1612	28 September 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1

U.S. Patent and Trademark Office — Part of Paper No.: 20190928

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/248,460	Maloney et al.
	Examiner	Art Unit
	BENJAMIN J PACKARD	1612

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	9	/	00

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE (Assistant Examiner) (Date)	Total Claims Allowed: 22	
/BENJAMIN J PACKARD/ Primary Examiner, Art Unit 1612 (Primary Examiner) 28 September 2019 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 1

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/248,460	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

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	22	
/BENJAMIN J PACKARD/ Primary Examiner, Art Unit 1612	28 September 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1

U.S. Patent and Trademark Office Part of Paper No.: 20190928

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/248,460	Maloney et al.
	Examiner	Art Unit
	BENJAMIN J PACKARD	1612

CPC - Searched*		
Symbol	**Date**	**Examiner**
A61K 9/0029	09/28/2019	BP
A61K 31/095	09/28/2019	BP
A61K 47/02	09/28/2019	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 inventor search	05/13/2019	BP
East search	05/13/2019	BP
CAPlus search- L-cysteine, impurities, aluminum, lead	05/13/2019	BP
East search	09/28/2019	BP
CA Plus search	09/28/2019	BP

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
A61K	9/0029, 31/095, 47/02	09/28/2019	BP

/BENJAMIN J PACKARD/ Primary Examiner, Art Unit 1612	/BENJAMIN J PACKARD/ Primary Examiner, Art Unit 1612

Bibliographic Data

Application No: 16/248,460

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.
01/15/2019	424	1612	066859/509450
RULE			

APPLICANTS

Exela Pharma Sciences, LLC, Lenoir, NC,

INVENTORS

John Maloney Salisbury, NC, UNITED STATES

Aruna Koganti Lenoir, NC, UNITED STATES

Phanesh Koneru Waxhaw, NC, UNITED STATES

CONTINUING DATA

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

02/06/2019

STATE OR COUNTRY

UNITED STATES

ADDRESS

ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000
UNITED STATES

FILING FEE RECEIVED

$6,060

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1133	A61K9/0029.cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2019/09/28 08:53
L2	3000	A61K31/095.cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2019/09/28 08:53
L3	34989	A61K47/02.cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2019/09/28 08:53
L8	39064	l1 or l2 or l3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2019/09/28 08:54
L9	2283	l8 and cysteine	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2019/09/28 08:54
L10	845	l9 and aluminum	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2019/09/28 08:54

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L11	93	A61K9/0029.cpc.	USPAT	AND	ON	2019/09/28 08:54
L12	280	A61K31/095.cpc.	USPAT	AND	ON	2019/09/28 08:54
L13	2728	A61K47/02.cpc.	USPAT	AND	ON	2019/09/28 08:55
L14	3090	l11 or l12 or l13	USPAT	AND	ON	2019/09/28 08:55
L15	102	l14 and cysteine.clm.	USPAT	AND	ON	2019/09/28 08:55
L16	7	l15 and aluminum.clm.	USPAT	AND	ON	2019/09/28 08:55

9/ 28/ 2019 8:55:58 AM
C:\ Users\ bpackard\ Documents\ EAST\ Workspaces\ 16248460-2.wsp

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 10/03/2019

ALSTON & BIRD LLP
BANK OF AMERICA 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.

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.

Bryan L. Skelton	(Typed or printed name)
/bryan l. skelton/	(Signature)
October 4, 2019	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/248,460	01/15/2019	John Maloney	066859/509450	6641

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	$1000	$0.00	$0.00	$1000	01/03/2020

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/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 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, NC

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. 16-0605

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 October 4, 2019

Typed or printed name Bryan L. Skelton Registration No. 50,893

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

Electronic Patent Application Fee Transmittal

Application Number:	16248460
Filing Date:	15-Jan-2019
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/Laura Tremont
Attorney Docket Number:	066859/509450

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1000	1000

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1000**

Electronic Acknowledgement Receipt

EFS ID:	37365858
Application Number:	16248460
International Application Number:	
Confirmation Number:	6641
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/Laura Tremont
Filer Authorized By:	Bryan Lee Skelton
Attorney Docket Number:	066859/509450
Receipt Date:	04-OCT-2019
Filing Date:	15-JAN-2019
Time Stamp:	10:51:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1000
RAM confirmation Number	E201904A53212644
Deposit Account	160605
Authorized User	Laura Tremont
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 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)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	509450_Issue_Fee_Transmittal.pdf	118893 8a161e7ec9d5e7454f3caa447190633cdc64b6d2	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30329 78de0ca5f6aad7129ba980823154ebc3eb0987a8	no	2
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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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/248,460	11/19/2019	10478453	066859/509450	6641

826 7590 10/30/2019

ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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 Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

John Maloney, Salisbury, NC;
Exela Pharma Sciences, LLC, Lenoir, NC
Aruna Koganti, Lenoir, NC;
Phanesh Koneru, Waxhaw, NC;

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court FOR THE DISTRICT OF DELAWARE on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT FOR THE DISTRICT OF DELAWARE
PLAINTIFF EXELA PHARMA SCIENCES, LLC		DEFENDANT AVADEL LEGACY PHARMACEUTICALS, LLC; and AVADEL US HOLDINGS, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 10,478,453	11/19/2019	Exela Pharma Sciences, LLC
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

Trials@uspto.gov
571-272-7822

Paper No. 12
Entered: November 18, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ETON PHARMACEUTICALS, INC,
Petitioner,

v.

EXELA PHARMA SCIENCES, LLC,
Patent Owner.

PGR2020-00064
Patent US 10,478,453 B1

Before ULRIKE W. JENKS, SUSAN L.C. MITCHELL, and CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge*.

DECISION
Denying Institution of Post-Grant Review
35 U.S.C. § 324

Eton Pharmaceuticals Inc. ("Petitioner") filed a Petition requesting a post-grant review of claims 1–22 ("the challenged claim") of Patent US 10,478,453 B1(Ex. 1001, "the '453 patent"). Paper 1 ("Pet."). Exela Pharma Sciences, LLC ("Patent Owner") filed a Preliminary Response to the Petition. Paper 6 ("Prelim. Resp."). With our authorization (Paper 7), Petitioner filed a reply to Patent Owner's Preliminary Response (Paper 9 ("Pet. Reply")), and Patent Owner filed a Sur-reply (Paper 11 ("Sur-reply")). We granted additional briefing to allow Petitioner to clarify the record with respect to assertions made in Patent Owner's preliminary response, and to allow Patent Owner the opportunity to address alleged conflicting arguments made in a related proceeding.

We have authority to determine whether to institute a post-grant review. 35 U.S.C. § 324. After considering all the papers submitted, for the reasons discussed below, we deny the Petition and do not institute a post-grant review.

I. BACKGROUND

A. Real Parties in Interest

Petitioner identifies itself as the real party in interest. Pet. 2. Patent Owner identifies itself as the real party in interest. Paper 3, 2.

B. Related Proceedings

Petitioner identifies as related matter *Exela Pharma Sciences, LLC v. Eton Pharms., Inc.*, Case No. 1:20-cv-00365-MN (D. Del., filed March 16, 2020) ("District Court Action"); *Exela Pharma Sciences LLC v. Avadel Legacy Pharms., LLC*, No. 1:20-cv-00024-MN (D. Del., filed January 7, 2020); *Exela Pharma Sciences LLC v. Sandoz Inc.*, Case No. 1:20-cv-00645-MN (D. Del., filed May 14, 2020); and *Exela Pharma Sciences LLC v.*

Sandoz Inc., Case No. 1:20-cv-01393 (D. Colo., filed May 15, 2020). Pet. 3; Paper 3, 1.

Petitioner also identifies U.S. Patent No. 10,583,155, U.S. Patent Appl. No. 16/746,028, U.S. Patent Appl. No.16/773,563 (now U.S. Patent No. 10,653,719), U.S. Patent Appl. No.16/773,641, U.S. Patent Appl. No.16/850,726, U.S. Patent Appl. No.16/850,962, and U.S. Patent Appl. No.16/850,973 as claiming benefit of priority to U.S. Application No. 16/248,460 which issued as the '453 patent. Pet. 3–4; Paper 3, 2.

C. The '453 Patent (Ex. 1001)

The '453 patent is titled "STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE." Ex. 1001, (54). The '453 patent issued from Application No. 16/248,460 ("the '460 application"), filed January 15, 2019. *Id.* at (21), (22).

The '453 patent describes 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, and aluminum in an amount from about 1.0 parts per billion (ppb) to about 250 ppb. *Id.* at (57).

"L-cysteine is a sulfur-containing amino acid that can be synthesized de novo from methionine and serine in adult humans." *Id.* at 1:14–16. Because L-cysteine can be synthesized by the body, it is considered a non-essential amino acid. *Id.* at 1:20. "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." *Id.* at 1:26–31.

According to the specification, "[i]t 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." *Id.* at 4:25–30. Moreover, the specification discloses that:

> [T]he 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.

Id. at 4:37–43.

The specification discloses that "known L-cysteine compositions contain up to 5000 ppb Aluminum." *Id.* at 7:8–9. In contrast, the specification describes "compositions that provide a therapeutically effective amount of L-cysteine, while containing less than 250 ppb Aluminum." *Id.* at 7:10–13. The specification discloses that reduced aluminum compositions "permit[ ] 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." *Id.* at 7:21–25.

The specification expressly defines the term "stable" as a composition that will contain the specified levels of all components, e.g., Aluminum, cystine, and pyruvic acid, "for [a] sufficient period of time to enable the composition to be commercially manufactured, stored, shipped, and administered in a clinical setting." *Id.* at 16:41–52. For example, the specification discloses compositions wherein "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." *Id.* at 25:6–9. The specification also discloses compositions wherein "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." *Id.* at 26:5–8.

D. Illustrative Claim

Claim 1 of the '453 patent is illustrative and reproduced below (with added bracketing for reference):

> A stable L-cysteine composition for parenteral administration, comprising:
>
> [(A)] 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;
>
> [(B)] Aluminum (Al) in an amount from about 1.0 parts per billion (ppb) to about 250 ppb;
>
> [(C)] L-cystine in an amount from about 0.001 wt% to about 2.0 wt % relative to L-cysteine;
>
> [(D)] pyruvic acid in an amount from about 0.001 wt% to about 2.0 wt % relative to L-cysteine;
>
> [(E)] a pharmaceutically acceptable carrier, comprising water;
>
> [(F)] headspace oxygen that is from about 0.5% v/v to 4.0% v/v from the time of manufacture to about 1 month from manufacture when stored at room temperature;
>
> [(G)] 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,
>
> [(H)] wherein the composition is enclosed in a single-use container having a volume of from about 10 mL to about 100 mL.

Ex. 1001, 59:2–25.

E. Prior art

Petitioner relies upon the following prior art references[1] (Pet. 6):

References	Patent / Publication	Exhibits
Sandoz Label	L-CYSTEINE HYDROCHLORIDE – cysteine hydrochloride injection, solution Sandoz Inc.	Ex. 1005
Hospira Label	AMINOSYN® A Crystalline Amino Acid Solution	Ex. 1009
Allergy Process	Exhibit A (Declaration of Harry "Warren" Johnson)	Ex. 1022

Petitioner relies on affidavits of Christopher Butler of the Internet Archive (Ex. 1004; Ex. 1010) and the attached exhibits to establish the availability of certain references.

F. Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–22 of the '453 patent on the following grounds (Pet. 6):

Ground	Claim(s) Challenged	Basis	Reference(s)
1	1–14	§ 103	The Sandoz Label in view of the knowledge of a person of ordinary skill in the art
2	15–20, 22	§ 103	The Sandoz Label and the Hospira Label, in view of the knowledge of a person of ordinary skill in the art
3	21	§ 103	The Sandoz Label and the Allergy Process, in view of the knowledge of a person of ordinary skill in the art

Petitioner also relies on the Declarations of Barrett Rabinow, Ph.D. (Ex. 1003) and Harry "Warren" Johnson (Ex. 1022) to support its assertions.

[1] Petitioner additionally cites references in support of "the knowledge of POSITA [(person of ordinary skill in the art)]." *See* Pet. 27–34.

Patent Owner relies on the Declaration of Robert J. Kuhn, PharmD (Ex. 2001) in support of its Patent Owner Preliminary Response.[2]

II. DISCUSSION

A. Overview of Petitioner's References

1.) "Sandoz Label" (Ex. 1005)

The Sandoz Label[3] describes a solution containing 50 mg of L-cysteine hydrochloride monohydrate, water, with the air replaced with nitrogen, and the solution having a pH 1.0–2.5. Ex. 1005, 5. The product comes in either 10 ml or 50 ml containers. *Id.* at 9. "L-Cysteine is a sulfur-containing amino acid. In premixed solutions of crystalline amino acids, cysteine is relatively unstable over time, eventually converting to insoluble cystine." *Id.* at 1. The indicated use of L-cysteine hydrochloride injection as described in the Sandoz Label is for dilution as an additive to crystalline amino acid injections to meet the intravenous amino acid nutritional requirements of infants receiving total parenteral nutrition. *Id.* at 2. The label describes that "[a]ny unused portion of the vial must be discarded within 4 hours after initial entry." *Id.* at 9.

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[2] To the extent a genuine issue of material fact arises from the testimony of Dr. Kuhn, we view that issue in the light most favorable to Petitioner solely for purposes of this Decision. *See* 37 C.F.R. § 42.108(c).

[3] Petitioner identifies "the Sandoz Label" as including the product, package insert, and package label. Pet. 1. Patent Owner contends that the "label" reaches three distinct sources of alleged prior art: the product itself, the package label, and the package insert (i.e. printed matter). Prelim. Resp. 29. Patent Owner contends that each source should be treated as a separate prior art. *Id.* at 31.

The label indicates that the product contains no more than 5000 mcg/L [(5000 ppb)[4]] of aluminum. The Sandoz Label provides a warning that the product contains aluminum that may be toxic. *Id.* at 2. "Research indicates that patients with impaired kidney function, including premature neonates, 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." *Id.*

2.) "Hospira Label" (Ex. 1009)

Hospira Label describes Aminosyn® as sterile crystalline amino acid solution for intravenous infusion. Ex. 1009, 1. Aminosyn provides crystalline amino acids to promote protein synthesis and wound healing and to reduce the rate of endogenous protein catabolism. *Id.* at. 2.

3.) "Allergy Process" from the Johnson Declaration (Ex. 1022)

Allergy Laboratories, Inc. ("Allergy"), manufactured the Sandoz product that is the subject of the Sandoz Label. Pet. 33 (citing Ex. 1022 ¶¶ 8–9). The Allergy Process[5] included the following steps:

a. Stirring water for injection, USP (WFI) in a vessel at temperature not more than (NMT) about 60°C;

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

c. Contacting the WFI with L-Cysteine Hydrochloride, Monohydrate, USP (L-Cysteine) for not longer than (NLT) 15 minutes;

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[4] 5000 mcg/L corresponds to 5,000 ppb. *See* Ex. 1003 ¶ 98; Ex. 2001 ¶ 20.
[5] Patent Owner contends that the Allergy Process does not qualify as prior art. *See* Prelim Resp. 19–28. Because we deny the Petition on the merits we do not address the prior art status of the Allergy Process.

d. Adjusting the pH, if needed, with concentrated Hydrochloric Acid, NF and/or 5.0N Sodium Hydroxide, NF;

e. Mixing for a minimum of about 10 minutes;

f. Capping the vessel and allowing to stand;

g. Filling said mixture into container of use;

h. Reducing the head space oxygen in said containers of use; and

i. Sealing said containers of use.

Pet. 33 (citing Ex. 1022 ¶¶ 16–18). The product made by the Allergy Process contained Aluminum at the very low end (e.g., typically < 100 ppb) of the no more than 5,000 mcg/L (i.e., ppb) range disclosed by the Sandoz Label. *Id.* (citing Ex. 1022 ¶ 15).

B. The Parties' Contentions

Petitioner contends that the challenged claims are obvious based primarily on the Sandoz Label. Pet. 43–72.

Petitioner's first obviousness ground, challenging claims 1–14, relies on the Sandoz Label in conjunction with the knowledge of a person of ordinary skill in the art.[6] Pet. 43. Petitioner contends that claim elements 1(A), 1(B), 1(E), and 1(H) are disclosed in the Sandoz Label. Pet. 44–47, 50.

[6] Petitioner identifies that the ordinary skilled artisan "would have had a Ph.D. in chemistry or biochemistry and at least 2 years of work experience with pharmaceutical drug product formulation analysis, development, optimization, and manufacture." Pet. 24. Patent Owner contends that Petitioner's definition misses the mark because it ignores the need for the artisan to also have "knowledge or experience in interpreting pharmaceutical drug labels or consulting with someone who did." Prelim. Resp.18. We note the parties' differences with respect to level of skill in the art, but because we deny institution for other reasons, we do not need to resolve this conflict here.

Petitioner concedes that elements 1(C), 1(D), 1(F), and 1(G) are not recited in the Sandoz Label, but contends that these elements would be obvious in light of the knowledge of a person of ordinary skill in the art. *See* Pet. 47 ("[T]he claimed ranges are the reasonably expected result of taking art-recognized steps to prevent oxidative degradation of L-Cysteine to L-Cystine during manufacture and storage." (citing Ex. 1003 ¶¶ 100–105)); 48 ("[T]he claimed range encompasses what was known in the art . . . ." (citing Ex. 1003 ¶¶ 107, 109–110; Ex. 1027, Ex. 1029), 49 ("[T]he claimed range encompasses dissolved oxygen levels known in the prior art . . . ." (citing Ex. 1003 ¶ 112; Ex. 1082)). With respect to independent claim 1, Petitioner contends that the skilled artisan would have relied on routine optimization using well-known techniques to achieve the reasonably expected result of preventing oxidative degradation of L-Cysteine. Pet. 49 (citing Ex. 1003 ¶ 113). Petitioner contends that dependent claims 2–14 would have similarly been obvious based on the Sandoz Label in conjunction with the knowledge of one of ordinary skill in the art and/or based on routine optimization. *See* Pet. 50–56 (citing Ex. 1003 ¶¶ 50, 54–58, 117–134, 136, 138, 139, 141–147, 150–156, 158; Ex. 1006; Ex. 1007; Ex. 1008; Ex. 1011; Ex. 1012; Ex. 1013; Ex. 1014; Ex. 1027; Ex. 1036; Ex. 1038; Ex. 1039; Ex. 1048; Ex. 1064; Ex. 1070; Ex. 1071).

Petitioner's second obviousness ground, challenging claims 15–20 and 22, relies on the Sandoz Label and the Hospira Label in conjunction with the knowledge of a person of ordinary skill in the art. Pet. 56–67. Petitioner contends that claim elements of claim 15 corresponding to claim elements 1(A), 1(B), 1(E), and 1(H) are disclosed in the Sandoz Label. Pet. 56–57. Petitioner contends that claim elements corresponding to additional

amino acid compositions as recited in claim 15 are taught by the Hospira Label. Petitioner concedes that the claim elements in claim 15 that correspond to claim elements 1(C), 1(D), 1(F), and 1(G) are not recited in the Sandoz Label, but contends that these elements would be obvious in light of the knowledge of a person of ordinary skill in the art. *See* Pet. 58–59.

Petitioner's third obviousness ground, challenging claim 21, relies on the Sandoz Label and the Allergy Process in conjunction with the knowledge of a person of ordinary skill in the art. Pet. 67–72 (citing Ex. 1003 ¶¶ 48–49, 195, 198–207; Ex. 1022 ¶ 16; Ex. 1027; Ex. 1028; Ex. 1031; Ex. 1032; Ex. 1033; Ex. 1036; Ex. 1041; Ex. 1069; Ex. 1082).

In response, Patent Owner argues that Petitioner is using additional references, specifically Waterman,[7] Yaman,[8] and Butler,[9] as more than just evidence of the knowledge of the person having ordinary skill in the art, but instead Petitioner is using these references to try and establish that specific claim elements were taught in the art. Prelim. Resp. 33 (citing *Adaptics Limited v. Perfect Company*, IPR2018-01596, Paper 20 at 20–23 (PTAB Mar. 6, 2019) (Informative Decision); *see also EnergySource Materials, LLC v. Terralithium LLC*, IPR2019-01605, Paper 7 at 30 (PTAB Apr. 6, 2020)). Waterman, Yaman, and Butler describe techniques for removing

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[7] Kenneth C. Waterman et al., *Stabilization of Pharmaceuticals to Oxidative Degradation*, 7 Pharm. Develop. & Tech, 1–32 (2002) (Ex. 1027).
[8] Alpaslan Yaman, *Chapter 7: Engineering Considerations in Sterile Powder Process, in Sterile Pharmaceutical Products: Process Engineering Application* (Kenneth. E. Avid ed., 1995) (Ex. 1029).
[9] Ian B. Butler et al., *Removal of Dissolved Oxygen from Water a Comparison of Four Common Techniques*, 41 Talenta 211–215 (1994) (Ex. 1082).

oxygen from either the headspace or from a liquid carrier as recited in claim elements 1(F) and 1(G). Patent Owner argues that, by taking a "catch-all" approach without identifying what specific combinations are intended and instead placing everything under the umbrella of either "routine optimization" or "knowledge of the ordinary artisan," the Petition lacks the required particularity that would allow Patent Owner a fair opportunity to formulate a response to the intended combinations. Prelim. Resp. 33 ("These 'back door' combinations should be rejected . . . .").

C. Claim Construction

Petitioner proposes constructions for two claim terms: "about" and "stable." *See* Pet. 25–26 (citing Ex. 1001, 16:40–51; 58:28–39). Patent Owner contends that there is no need to resolve any claim construction terms, but notes that the term "stable" requires that the composition must be stable over certain minimum time period. Prelim Resp. 18.

Because this decision declining to institute trial does not turn on the adoption of any particular claim construction we need not construe any terms. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (noting that "we need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

D. Analysis

1.) Particularity Requirement

The relevant statute provides that a determination whether to institute a post-grant review shall be made based on "the information presented in the petition." 35 U.S.C. § 324(a). Under 35 U.S.C. § 324(a), a post-grant review

can be instituted only if it is more likely than not that the petitioner would prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 324(a). In addition, 35 U.S.C. § 322(a)(3) provides that the petition identify "in writing and with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim." Section § 42.22(a)(2) of Title 37 of the US Code of Federal Regulations provides that each petition includes, "[a] full statement of the reasons for the relief requested, including a detailed explanation of the significance of the evidence including material facts, and the governing law, rules, and precedent." *See also* 37 C.F.R. § 42.204.

In a post-grant review, as in an *inter partes* review, "the petitioner has the burden from the onset to *show with particularity* why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (emphasis added) (citing 35 U.S.C. §312(a)(3) as applied to *inter partes* review, which is equivalent to the 35 U.S.C. §322(a)(3) as applied to post-grant review). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015); *see also In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375–78 (Fed. Cir. 2016) (discussing the burden of proof in AIA trials).

Consistent with the statute and case law, our Consolidated Trial Practice Guide[10] advises that petitioners should "avoid submitting a

[10] Consolidated Trial Practice Guide Update, 59 (Nov. 2019), available at www.uspto.gov/trialpracticeguideconsolidated, ("TPG").

repository of all the information that a judge could possibly consider, and instead focus on concise, well-organized, easy-to-follow arguments supported by readily identifiable evidence of record." TPG 39.

In this case, we agree with Patent Owner that the Petition suffers from a lack of particularity because it is not clear what aspects of the numerous references cited in the body of the Petition, but not listed in the grounds of unpatentability, Petitioner relies on to establish a basis for "routine optimization" as the reason for arriving at claim elements 1(C), 1(D), 1(F), and 1(G). By not including references in the formulation of the ground unpatentability Petitioner is not providing an articulated reason that allows Patent Owner the ability to respond and leaves Patent Owner, and the Board for that matter, to guess how the references are applied to each particular ground. Prelim. Resp. 33 ("[Petitioner] is relying on its 'additional references' to create back-up obviousness combinations without identifying those combinations to Exela and the Board." (emphasis omitted)); *cf. In re Hoch*, 428 F.2d 1341, 1342 n.3 (CCPA 1970) ("Where a reference is relied on to support a rejection, whether or not in a 'minor capacity,' there would appear to be no excuse for not positively including the reference in the statement of rejection.").

Petitioner relies on the Sandoz Label in conjunction with the knowledge of a person of ordinary skill in the art to arrive at the L-cysteine composition as recited in independent claim 1. *See* Pet. 43–50. Patent Owner argues that Petitioner relies on more than the general knowledge of the ordinary artisan because Petitioner uses Waterman and Yaman to establish a headspace oxygen range that meets the claim requirements, yet does not

recite these references in the stated ground of unpatentability. Prelim Resp. 32 (citing Ex. 1027 and Ex. 1029).

For example, Petitioner contends that the oxygen sensitivity of L-cysteine is well-known in the art and easily addressed. *See* Pet. 38–40. Petitioner notes that in "the Sandoz Label, headspace air is replaced with nitrogen to address L-Cysteine's oxygen sensitivity." Pet. 39 (citing Ex. 1003 ¶ 31; Ex. 1005, 1), 48 (citing Ex. 1003 ¶ 109; Ex. 1029, 41; Ex. 1027, 27). Petitioner then notes that given the disclosure of the Sandoz Label in conjunction with teachings in Yaman and Waterman, "the percent oxygen in the vial headspace" of the Sandoz Label encompasses the claimed range based on what was known in the art. Pet. 48. Here, the Petition cites Yaman and Waterman to establish the oxygen level in the headspace of the product described in the Sandoz Label. *Id.* (citing Ex. 1003 ¶¶ 107–108). The Petition, however, does not cite these references in the ground of unpatentability, and instead, Petitioner appears to be relying on routine optimization based on the knowledge of one of ordinary skill in the art to arrive at the conclusion that the Sandoz Label meets the claimed elements.

Another example of Petitioner's reliance on more than just the knowledge of the ordinary artisan is with respect to the dissolved oxygen range in water as disclosed in Butler. *See* Pet. 49 (citing Ex. 1082), Prelim Resp. 32 (citing Ex. 1082). Butler describes several techniques to remove dissolved oxygen from a liquid. These are: purging with nitrogen, argon, or a similar inert gas; boiling at 1 atm; sonication under "vacuum"; and boiling under "vacuum." Ex. 1082, 1. Butler concludes that a nitrogen purge is an efficient method for removing dissolved oxygen from deionized water but concludes "it is a poor method to preserve solutions containing redox-

sensitive species." *Id.* at 5. Here, Petitioner acknowledges that the Sandoz Label does not disclose dissolved oxygen content in the carrier, but finds that purging with nitrogen is a known way to reduce oxygen levels. Pet. 49 (citing Ex. 1003 ¶ 112; Ex. 1082, 1; Ex. 1069, 1; Ex. 1032 at 17–18; Ex. 1033, 13; Ex. 1027, 27). There is nothing in the Sandoz Label that suggests that the carrier was purged with nitrogen. Thus, Petitioner is relying on teachings in Waterman, Butler, and others to establish an oxygen range for water and a reason to reduce the oxygen content in the liquid carrier of the product described in the Sandoz Label. *Id.* (citing Ex. 1003 ¶¶ 111–113). Again, rather than citing these references in the ground of unpatentability, which necessitates articulating a rationale to combine the teachings of the references with a reasonable expectation of success, Petitioner instead is relying on routine optimization based on the insufficiently articulated knowledge of one of ordinary skill in the art to arrive at the conclusion that the Sandoz Label meets the claimed elements.

Petitioner contends that "L-Cysteine was known to oxidatively degrade to L-Cystine, which can form undesired particulate matter." Pet. 46 (citing Ex. 1003 ¶ 42; Ex. 1020 at 3; Ex. 1031 at 2; Ex. 1061 at 1–2). Patent Owner argues that Petitioner has not demonstrated that the oxidative behavior of L-cysteine in the pH range of 1.0–2.5 as listed on the Sandoz Label converts the L-cysteine to the unwanted cystine. Prelim. Resp. 47 (citing Ex. 1020, 3 ("In neutral or slightly alkaline aqueous solutions, [cysteine hydrochloride] is oxidized to cystine by air. It is more stable in acidic solutions."). Patent Owner contends that the Petition has not articulated a reason why a person having ordinary skill in the art would have sought to reduce aluminum concentrations by optimizing the cystine levels

in a composition that has the recited low pH. *Id.* 49. In other words, Patent Owner's contention is that Petitioner has not explained why one of ordinary skill in the art would have thought that cystine levels would have had any bearing on the aluminum content of the composition. We agree with Patent Owner that the Petition does not sufficiently explained why one of ordinary skill in the art would want to look at cystine levels in the product disclosed in the Sandoz Label in the first place and what reason there is to maintain it within the recited range.

Based on the above examples, we agree with Patent Owner and find that the Petition fails to meet the particularity requirement of 35 U.S.C. § 322(a)(3) with regard to Petitioner's assertion that the subject matter of claims 1–14 would have been obvious over the Sandoz Label in conjunction with the knowledge of a person of ordinary skill in the art, and we decline to institute a post-grant review on that ground. We also decline to identify and analyze all possible permutations of prior art combinations that Petitioner may have sought to include in this ground but did not expressly articulate.

2.) Routine Optimization

According to Petitioner, the Sandoz Label already warns that aluminum may be toxic to certain patient populations. Pet. 44. Petitioner contends that in response to FDA regulatory demand, articulated market pressures, and recognized toxicity, there was a motivation to lower the aluminum content in total parenteral nutrition (TPN) solutions. Pet. 35. As recognized in the prior art:

> [T]o limit the risk of aluminum toxicity, the U.S. Food and Drug Administration (FDA) modified its "Regulations on Aluminum in Large and Small Volume Parenterals Used in Total Parental Nutrition" with the January 2000 Final Rule,

> enacted in July 2004. The Final Rule limits the aluminum concentration of large-volume parenteral products to 25 mcg/L . . . and a recommended maximum daily aluminum dose of 4 to 5 mcg/kg/ day to prevent accumulation and toxicity

Ex. 1007, 2 (citations omitted). The FDA in communication with Patent Owner indicated that the aluminum dose associated with the L-cysteine drug product in their new drug application "should be limited to ≤ 0.6 mcg/kg/day. To comply with this dose level, a limit of ≤ 145 mcg/L aluminum is needed." Ex. 1019, 1. This aluminum level in the FDA demand is even lower than the previously recited aluminum dose for parenteral nutrition enacted in July 2004. *Compare* Ex. 1019, 1 (aluminum limited to limited to ≤ 0.6 mcg/kg/day) *with* Ex. 1007, 2 (aluminum dose of 4 to 5 mcg/kg/ day). The letter to Patent Owner also noted that due to the extremely low pH of their drug product, pH 1–2.5, it is also necessary to assess the leachables/extractables from any new container Exela Pharma Sciences may wish to use. Ex. 1009, 2. Based on these disclosures, we agree with Petitioner that the evidence supports the position that there is motivation to lower aluminum contamination in total parenteral nutritional solutions, specifically, to avoid aluminum toxicity.

Motivation alone, however, is not sufficient for reaching a conclusion of obviousness. Obviousness also requires a reasonable expectation of success. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). As Patent Owner argues, Petitioner's reliance on the FDA regulation regarding aluminum threshold goal does not say anything about *how* to achieve the goal. Prelim. Resp. 61. In other words, knowing the FDA's goal may provide a motivation to try and lower aluminum levels in total parenteral nutritional supplements but that does not

provide a path of how to achieve the stated goal. Prelim Resp. 61–62 (citing *Endo Pharm. Inc. v. ActavisLLC*, 922 F.3d 1365, 1376 (Fed. Cir. 2019) (finding that FDA communications did not show a reasonable expectation of success where they merely "recite[d] a goal without teaching how the goal is attained"); *In re Cyclobenzaprine HCl Extended Release Capsule Patent Litig.*, 676 F.3d 1063, 1074 (Fed. Cir. 2013) (reversing obviousness determination and rejecting district court's reliance on FDA guidance document about approval requirements for extended-release formulations because "'knowledge of the goal does not render its achievement obvious'" (quoting *Abbott Labs, Inc. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2009))). To be sure, "[o]bviousness does not require absolute predictability of success." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). But it is also not permissible to reach an obviousness conclusion by allowing each of numerous possible choices to be tried until one possibly arrived at a successful result. *See id.*

Petitioner attempts to further bolster its routine optimization argument by urging that the recitation of "[c]ontains no more than 5,000 mcg/L of . . . aluminum" in the Sandoz Label should be interpreted as a disclosure of an aluminum range from 0 to 5000 ppb. Pet. 44–45 (citing Ex. 1003 ¶ 32; Ex. 1005, 5, 10). Based on this interpretation, Petitioner concludes that it would have been obvious to optimize the aluminum content in a parenteral solution. *Id.* (citing *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); *ClearValue, Inc. v. Pearl Rivers Polymers, Inc.*, 668 F.3d 1340, 1345 (Fed. Cir. 2012)).

Patent Owner argues that "[a] pharmacist reading the label would treat it as disclosing a maximum aluminum content of 5,000 ppb (mcg/L)

aluminum, and would have used this value to prepare a formulation for administration to an infant." Prelim. Resp. 63. Patent Owner's expert, Dr. Kuhn, avers that it was known

> that for L-cysteine hydrochloride solutions packaged in glass the aluminum content will increase over time. . . . Ideally, L-cysteine hydrochloride solutions with a longer remaining shelf life would be used for neonatal patients because their aluminum levels might be lower than products with a shorter remaining shelf life (i.e., closer to their expiration date).

Ex. 2001 ¶ 22.

It is known that

> Aluminum is a contaminant in all parenteral nutrition solutions. Manufacturers currently label these products with the maximum aluminum content at the time of expiry, but there are no published data to establish the actual measured concentration of aluminum in parenteral nutrition solution products prior to being compounded in the clinical setting.

Ex. 1007, 1.

Here, the evidence supports the position that the Sandoz product label recites the contamination level at the expiration date. Even if the concentration of the aluminum level before that date is actually lower, the evidence in the record does not support the position that the Sandoz Label teaches the aluminum concentration in the product to be zero or even within the claimed range of 1 to 250 ppb.

The evidence of record shows that it was known in the art that

> [a]mino acids complex metals; the aluminium complexes of glutamic and aspartic acids have known stability constants, and although the stability constant for cys-Al is not found in the literature, cysteine must interact with Al as it interacts with other metals; this could explain its great leaching action on the aluminium present in glass. . . . Cysteine is a ligand for

> aluminium [and the affinity is] as strong[] as citrate or oxalate.

Ex. 1008, 4. Thus, when glass containers are used for storing cysteine as well as its oxidation product cystine, the aluminum concentration in the solution continues to increase during storage. *Id.* at 5.

> Aluminum contamination in products comes from many sources.
>
> The results of all investigated container materials revealed an aluminium content of 1.57% Al in glass, 0.05% in plastic and 4.54% in rubber. The sterilization procedure showed that even pure water was able to extract Al from glass and rubber, 22.5 ± 13.3 µg/L and 79.4 ±22.7 µg/L respectively, while from plastic the [amount of] aluminium leached was insignificant.

Ex. 1012, Abstract.

We agree with Patent Owner that the recitation of "contains no more than 5000 mcg/ml (i.e. 5000 ppm) aluminum" is reasonably interpreted to be the upper end of the aluminum concentration that is expected in the product. We also do not find that zero is a reasonable starting point for the aluminum concentration in a cysteine containing composition based on the record before us. Here, the Sandoz product even right after manufacture contains measurable aluminum, indicating that the level of aluminum in the product is not zero at any time. *See e.g.* Ex. 1022[11] ¶ 15 ("L-Cysteine Products (*i.e.*, within several weeks of manufacture) were typically below about 100 ppb."), Exhibit B (showing aluminum concentration of as high as 61 ppb after manufacture)). The evidence, therefore, does not support Petitioner's

[11] In this decision, we accept the disclosures for the matter asserted in the Johnson declaration (Ex. 1022). We do not address whether the disclosure of the Allergy Process presented in the Johnson declaration qualifies as prior art based on the sale of the product or whether the process qualifies as prior art under public use. *See* Pet. Reply. 6; Pet. 9.

position that "the Sandoz product contained aluminum in the range of 0 ppb to 5,000 ppb." Pet. 40–41 (citing Ex. 1003 ¶ 32; Ex. 1005, 5). Because we do not find that the product described in the Sandoz Label discloses a range for aluminum from 0 ppb to 5,000 ppb, we are not persuaded by Petitioner's position that there is a reasonable expectation that routine optimization would lead to aluminum concentrations as recited in claim 1 of the '453 patent based on optimizing overlapping ranges. *See* Pet. 42.

On this record, we agree with Patent Owner that Petitioner has not provided a sufficient evidentiary basis from which to conclude that there is a reasonable expectation for making L-cysteine containing solutions having the requisite aluminum content as recited in claim 1 of the '453 patent. With respect to claims 2–14, Petitioner relies on the same underlying arguments as presented for claim 1 that we find unpersuasive.

3.) Second and Third Grounds

The second ground of unpatentability as recited in the Petition relies on the addition of the Hospira Label with the Sandoz Label in conjunction with the knowledge of a person of ordinary skill in the art. *See* Pet. 56–67. The addition of the Hospira Label does not address the underlying issue as discussed above for ground 1, specifically, that the Sandoz Label does not disclose a range of aluminum contamination from 0 ppb to 5,000 ppb. Because the Hospira Label is not relied upon to rectify the underlying shortcoming of the Sandoz Label (*see above* II.D.1 and II.D.2), we conclude that the evidence presented in the Petition does not support the contention that the claims 15–20 are 22 are unpatentable.

The third ground of unpatentability as recited in the Petition relies on the addition of the Allergy Product with the Sandoz Label in conjunction

with the knowledge of a person of ordinary skill in the art. *See* Pet. 67–72. The Allergy Product is not relied upon to rectify the underlying shortcoming of the Sandoz Label (*see above* II.D.1 and II.D.2), and therefore, we conclude that the evidence does not support Petitioner's contention that the claim 21 is unpatentable.

III. CONCLUSION

For the foregoing reasons, we are not persuaded that the Petition establishes that it is "more likely than not" that any of claims 1–22 of the '453 patent are unpatentable under 35 U.S.C. § 103(a) based on the grounds presented. We, therefore, do not institute a post-grant review of those challenged claims based on the current Petition.

IV. ORDER

Accordingly, it is:

ORDERED that the Petition is denied and no trial is instituted.

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AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
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DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	5/14/2020	FOR THE DISTRICT OF DELAWARE

PLAINTIFF	DEFENDANT
EXELA PHARMA SCIENCES, LLC	SANDOZ, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	10,478,453	11/19/2019	Exela Pharma Sciences, LLC
2	10,583,155	3/10/2020	Exela Pharma Sciences, LLC
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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	3/16/2020	FOR THE DISTRICT OF DELAWARE

PLAINTIFF	DEFENDANT
EXELA PHARMA SCIENCES, LLC	ETON PHARMACEUTICALS, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	10,478,453	11/19/2019	Exela Pharma Sciences, LLC
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DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/16/2020	FOR THE DISTRICT OF DELAWARE

PLAINTIFF	DEFENDANT
EXELA PHARMA SCIENCES, LLC	ETON PHARMACEUTICALS, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:20-cv-00365 MN	4/14/2021	for the District of Delaware

PLAINTIFF	DEFENDANT
EXELA PHARMA SCIENCES, LLC	ETON PHARMACEUTICALS, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	10,478,453	11/19/2019	Exela Pharma Sceinces, LLC
2	10,583,155	3/10/2020	Exela Pharma Sciences, LLC
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DATE INCLUDED 7/28/2020 & 4/14/2021

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	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	~~10,653,719~~	~~5/19/2020~~	~~EXELA PHARMA SCIENCES, LLC(Incl. 7/28/2020; Amd.Cmp)~~ *
2	10,905,713	2/2/2021	EXELA PHARMA SCIENCES, LLC (Incl. 4/14/2021; 2d Amd.Cmp)
3	10,912,795	2/9/2021	EXELA PHARMA SCIENCES, LLC (Incl. 4/14/2021; 2d Amd.Cmp)
4	10,933,089	3/2/2021	EXELA PHARMA SCIENCES, LLC (Incl. 4/14/2021; 2d Amd.Cmp)
5			

* Dismissed from suit by D.I. 152 Stipulation and Order dated 9/24/2021.

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DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/16/2020 (Format m/d/yyyy)	FOR THE DISTRICT OF DELAWARE

PLAINTIFF	DEFENDANT
EXELA PHARMA SCIENCES, LLC	ETON PHARMACEUTICALS, INC.

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DECISION/JUDGEMENT
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