

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	209379
Priority or Standard	Priority
Submit Date(s)	7/3/2018
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PDUFA Goal Date	4/30/2019
Division/Office	DGIEP
Review Completion Date	4/30/2019
Established/Proper Name	Selenious Acid
(Proposed) Trade Name	Selenious Acid
Pharmacologic Class	Trace Element
Code name	
Applicant	American Regent, Inc.
Dosage form	Injection (98 mcg equivalent to 60 mcg selenium/ml)
Applicant proposed Dosing Regimen	(b) (4) kg: 2 mcg/kg/day (b) (4) kg: (b) (4) mcg/day (b) (4) 60 mcg/day
Applicant Proposed Indication(s)/Population(s)	Source of selenium for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated in adult and pediatric patients
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Source of selenium for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated in adult and pediatric patients
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	<7Kg: 2 to 4 mcg/kg/day ≥7kg: 2 mcg/kg/day (up to 60 mcg/day) Adults: 60mcg/day

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OPQ = Office of Pharmaceutical Quality

OPDP = Office of Prescription Drug Promotion

OSE = Office of Surveillance and Epidemiology

SRPM = Safety Regulatory Project Management

DEPI = Division of Epidemiology

DMEPA = Division of Medication Error Prevention and Analysis

DPV = Division of Pharmacovigilance

DRISK = Division of Risk Management

OPT = Office of Pediatric Therapeutics

OULDC = Office of Unapproved Drug and Labeling Compliance

DPMH = Division of Pediatric and Maternal Health

DSS = Drug Shortage Staff

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse events
AI	adequate intake
ASPEN	American Society of Parenteral and Enteral Nutrition
BLA	biologics license application
CAERS	CFSAN Adverse Event Reporting System
CFR	Code of Federal Regulations
CFSAN	Center for Food Safety and Applied Nutrition
CKD	chronic kidney disease
CRP	C-reactive protein
DEPI	Division of Epidemiology
DGIEP	Division of Gastroenterology and Inborne Errors Products
DHOT	Division of Hematology Oncology Toxicology
DMF	drug master file
DPMH	Division of Pediatric and Maternal Health
DPV-I	Division of Pharmacovigilance I
EAR	Estimated Average Requirement
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GA	gestational age
GSHPx	glutathione peroxidase
HD	hemodialysis
HED	human equivalent dose
HPLC-DAD	high performance liquid chromatography-diode array detection
HPN	home parenteral nutrition
ICH	International Conference on Harmonization
IOM	Institute of Medicine
LOAEL	Lowest Observed Adverse Effect Level
NADPH	nicotinamide adenine dinucleotide phosphate
(b) (4)	(b) (4)
NDA	new drug application
NOAEL	no-observed-adverse-effect level
OECD	Organization for Economic Co-operation and Development
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PDE	permitted daily exposure
PD	pharmacodynamics
PK	pharmacokinetics
PMR	postmarketing requirement
PN	parenteral nutrition

PREA	Pediatric Research Equity Act
RBC	red blood cell
RDA	Recommended Dietary Allowance
RDI	Reference Daily Intake
REMS	risk evaluation and mitigation strategy
RH	relative humidity
Se	Selenium
SIDS	Screening Information DataSet
SLR	systematic literature review
TE	trace element
TOC	Total Organic Carbon
TPN	total parenteral nutrition
UL	Tolerable Upper Intake Level
USP	U. S. Pharmacopeia
VLBW	very low birth weight

1. Executive Summary

1.1. Product Introduction

The product under review, Selenious Acid Injection, is a new chemical entity (NCE). Selenious acid is the acid form of sodium selenite, an inorganic source of elemental selenium. Selenium is an essential trace element necessary in the diet to maintain health.

Selenious Acid Injection provides 60 mcg/mL of elemental selenium. The product will be supplied as a Pharmacy Bulk Package 10 mL vial intended for admixture with parenteral nutrition (PN) and not for direct intravenous administration. The Applicant, American Regent (formerly known as Luitpold Pharmaceuticals), is not proposing a proprietary name. The Established Pharmacologic Class will be “trace element”.

The proposed indication for Selenious Acid Injection is a “source of selenium in parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.” The indication is for adults and pediatric patients (birth to <17 years of age).

The Food and Drug Administration (FDA) has not previously approved any products containing selenious acid. However, the Applicant currently markets “Selenium Injection” (containing 40 mcg/mL of elemental selenium) as an unapproved product which has been used for close to 30 years for the following indication “as a supplement to intravenous solutions given for total parenteral nutrition (TPN). Administration of selenium in TPN solutions helps to maintain plasma selenium levels and to prevent depletion of endogenous stores and subsequent deficiency symptoms.”[1] Selenious acid is also marketed, unapproved by the Applicant in a fixed-combination trace element product (Multi-Trace 5: chromic chloride, cupric sulfate, manganese sulfate, selenious acid, and zinc sulfate heptahydrate).

Oral selenium is marketed as a dietary supplement per 21 CFR 10.9 that provides its RDI (Reference Daily Intake) value.

The Applicant has proposed a dosing regimen of: 2 to 4 mcg/kg/day in [REDACTED] pediatric patients weighing less than [REDACTED] kg; [REDACTED] mcg/kg/day in pediatric patients weighing [REDACTED] kg, and 60 mcg/day in adults [REDACTED].

As described in later sections, the Applicant revised their proposed pediatric dosing regimen during the review cycle and the review team recommended further revisions to the pediatric dosage regimen (see Section 10 Pediatrics). See Section 8.4 for the dosage regimen recommended for approval.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Selenium is considered an essential trace element (TE) which functions as a key component of catalytic enzymes for various cellular activities and structural proteins required for human health. Inadequate selenium intake can lead to deficiency and has been associated with cardiomyopathy, muscle weakness, nail changes, etc. The Applicant submitted a literature-based 505(b)(2) application without conducting clinical trials. Support for efficacy is based on published literature reporting on consistent selenium exposures based on clinical trials of intravenous selenious acid or selenite (disodium salt of selenious acid) in the PN setting, that evaluated doses of 32 – 400 mcg/day, along with nutritional requirements of oral/enteral selenium i.e., Recommended Dietary Allowance or Reference Daily Intake (RDA, RDI) values, parenteral nutrition (PN) guidelines based on expert consensus, time and extent of use in clinical practice, as well as generally accepted scientific knowledge of selenium as an essential trace element. Taken together, these support a finding of substantial evidence of effectiveness of Selenious Acid Injection, for the proposed indication in adult and pediatric patients as a “source of selenium in parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated.”

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Selenium is an essential trace element naturally present in many foods and is a constituent of more than 35 selenoproteins that play critical roles in reproduction, thyroid hormone metabolism, DNA synthesis, and protection from oxidative damage and infection. It is currently marketed as an oral dietary supplement with an oral Reference Daily Intake (RDI) value of 55 mcg/day for adults per 21 CFR 101.9. The proposed product, Selenious Acid Injection, USP, is a 60 mcg/mL solution for intravenous use intended as a source of selenium in PN when oral or enteral nutrition is not possible, insufficient, or contraindicated. As the sole parenteral source, selenious acid products marketed unapproved since 1990 with the same active ingredient as the proposed product are vulnerable to drug shortage and have frequently been on the drug shortage list since 2012.

Parenteral nutrition (PN) without supplementation of selenium is likely to result in clinical deficiency. Selenium deficiency is the basis for the essential nature of selenium as a dietary nutrient for humans and affects 500 million to 1 billion people worldwide secondary to inadequate dietary intake [2]. While selenium deficiency can occur where selenium content in the soil and consequently plant sources is lowest, its occurrence is rare in the United States.

A variety of clinical presentations have been observed with selenium deficiency, largely due to the wide range of biochemical and physiologic functions that require selenium. Clinical presentations, notable in many case reports of selenium deficiency during PN, include fatal or reversible cardiomyopathy, skeletal muscle myopathy, hair and nail abnormalities and macrocytic anemia. In the United States, most cases of selenium depletion or deficiency are associated with severe gastrointestinal problems, such as Crohn's disease, a result of impaired selenium absorption. One interesting feature of selenium deficiency is that it does not usually cause illness by itself but can make the body more susceptible to illnesses caused by other nutritional, biochemical, or infectious stresses required to provoke the overt symptoms of deficiency.

The efficacy and safety of Selenious Acid Injection has been based on data from a systematic literature review (SLR) commissioned by the Applicant and conducted by the (b) (4) (b) (4) identified 58 publications reporting on selenium exposure in adults and 14 in pediatric populations, including randomized, placebo- and active-controlled clinical trials in a range of patient populations (neonatal, pediatric, and adult), that primarily evaluated the effect of intravenous selenium supplementation in patients on chronic PN. An additional 51 publications not captured by (b) (4) based on an independent assessment of the SLR was identified during the NDA review. The published studies are largely uncontrolled with noted variability in study design, data collection, or analysis, dosing, efficacy and safety

assessments as well as were conducted in heterogeneous populations; however, the time and extent of parenteral selenium use in clinical practice for supplementation purposes was taken into consideration.

Two, non-randomized, controlled studies [3, 4] in adults with chronic gastrointestinal diseases who were on TPN studied effects of doses of 80 to 200 mcg/day of parenteral selenium. One study assessed the effects of increasing doses of selenium on selenium concentrations while the second study compared various parameters that could be used as indicators of selenium concentrations in long-term PN patients after administration and withdrawal of parenteral selenious acid. In the Lane et al study, adult patients received 0, 80 or 160 mcg/day for 1 month with an assessment of maintaining normal selenium concentrations within the study reference range compared to healthy controls. Study patients on 160 mcg/day were then decreased to 80 mcg/day during the study and still maintained selenium levels within the reference range. Per the second study, platelet glutathione peroxidase activity was the most sensitive index of selenium status.

Two, randomized, controlled studies [5, 6] in preterm patients supported that a 3 mcg/kg/day dose maintained serum selenium levels within the reference range in one study whereas in the second study, a 1.5 mcg/kg/day dose in very low birth weight infants did not.

The proposed indication and dosing are supported by the following supplemental information:

- Standard oral/enteral nutritional requirements, developed by the Food and Nutrition Board at the Institute of Medicine (IOM) of the National Academies, which vary by age and sex (i.e., Recommended Dietary Allowance or Intake (RDA, RDI) values; average daily level of intake sufficient to meet the nutrient requirements of nearly all (97% to 98%) healthy individuals: 55 mcg/day in adults, 70 mcg/day in pregnant and lactating females and 15 to 55 mcg/day in pediatric patients.
- Average daily selenium intake in Americans aged 2 years and older from foods is 108.5 mcg and from both foods and supplements is 120.8 mcg according to an analysis of data from the National Health and Nutrition Examination Survey
- Standard adult enteral formulas contain 62 to 110 mcg selenium
- Human milk studies estimate oral daily requirement in infants is 2 mcg/kg/day
- FDA requirement for infant formula to contain 2 to 7 mcg of selenium/100 kilocalories (21CFR107.100)
- Oral bioavailability of selenium is estimated to be an average of about 70% (range 44 to >90%)
- Lower baseline selenium levels in PN-dependent patients compared to healthy controls across observational studies; 16% to 75% of selenium-supplemented PN patients had selenium levels below the reference range. However, the severity of underlying illnesses

necessitating PN, doses administered, and selenium concentrations prior to enrollment in these studies were not always reported.

Clinical significance of these findings is uncertain as evidence of clinical deficiency was not reported.

- Current ASPEN guidelines based on expert consensus recommend 60 to 100 mcg/day in adults and 2 mcg/kg/day in pediatric patients
- Time and extent of use in clinical practice

None of the published studies established effectiveness of Selenium Acid Injection based on a clinical outcome measure and given the 'source' indication, no clinical outcome claims were included in the proposed indication. Consistent increase and/or maintenance of selenium concentrations with parenteral selenium administration, the role of normal selenium levels in preventing deficiency-associated conditions, together with its oral RDI, bioavailability (oral and iv) information, as well as generally accepted scientific knowledge of selenium's role in maintaining optimal health support a finding of substantial evidence of effectiveness for the proposed indication. A range of selenium doses may be needed to achieve individual nutritional requirements.

There are no reports of toxicity secondary to parenteral supplementation of selenium to meet dietary requirements in adult or pediatric populations. Acute and chronic toxicities due to oral ingestion of large quantities of selenium have been reported primarily in the adult literature [7-11]. Signs and symptoms of selenium toxicity including alopecia, hair and nail changes, skin rash, gastrointestinal disturbances, "garlic" breath odor, electrocardiogram changes, and nervous system abnormalities at doses greater than 1 gram. Cardiopulmonary arrest and death have been reported with oral ingestions of 10 grams [12]. The IOM has established the Tolerable Upper Limit (UL), No Observed Adverse Effect Level (NOAEL) and the Lowest Observed Adverse Effect Level (LOAEL) for selenium at doses of 400, 800 and 913 mcg/day in adults, respectively [13].

The remaining areas of uncertainties include insufficient or inconclusive human data in special populations such as patients with burns, critical illness and pre-term neonates, who may require higher doses of selenium to achieve their dietary requirements.

Based on the collective evidence, the safety and effectiveness of Selenium Acid Injection have been established. While the Applicant proposed a 60 mcg/day dose in adults for labeling with a plan to allow physician-discretion for dose adjustments based on individual variability, the CDTL interprets the preponderance of evidence to support doses including and higher than the 60 mcg/day. A dosing range of 60 to 100 mcg/day may be more physiologically appropriate as it replicates the amount of selenium obtained through a normal diet and would address the inherent increased requirements of patients on PN as evidenced by the proportion of chronic PN patients with selenium levels lower than that of healthy controls and below the reference range. Range-based dosing would also assure awareness by practicing physicians of the need for basal requirements beyond 60 mcg/day in PN patients to optimize function of the various selenoproteins and is the approach utilized for many other components of TPN based on laboratory results, underlying disorders, or other factors such as metabolic requirements. In addition, a dosing range would ensure that doses necessary for solely meeting source requirements would be below those reported in the literature to correct deficiency. While the CDTL supports a dosing range for adults, the Division has decided on an approach to approve the proposed 60 mcg/day dose for adults and allow physicians to adjust doses based on an assessment of individual needs. This approach considered the amount of evidence supporting 60 mcg/day, with administration of higher doses as dictated by monitoring of selenium concentrations during treatment. The Applicant has proposed 2 to 4 mcg/kg/day for (b) (4) pediatric population (b) (4) a weight-based approach [Pediatric Patients equal to or greater than 7kg: 2 mcg/kg/day (up to 60 mcg/day) and Pediatric Patients less than 7kg: 2- 4 mcg/kg/day] is recommended for approval to ensure the selenium requirements of the lightest patients are met.

Refer to Deputy Director memo – Section 14 for additional discussion.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none">Se is an essential trace element obtained primarily through diet required for essential metabolic processes in human health.Deficiency in dietary Se has been epidemiologically linked to clinical syndromes that include cardiomyopathy, skeletal muscle myopathy, and nail and hair changes. In infants on chronic TPN, Se deficiency may cause alopecia and growth retardation.Based on literature that evaluated selenium concentrations in patients receiving parenteral selenium, a broad proportion of patients (16 to 75%) receiving selenium supplementation at doses of 40 to 60, 63, and 69 mcg/day had levels below the normal reference range and were potentially not achieving their nutritional requirements. However, the severity of underlying illnesses necessitating PN, doses administered, and selenium concentrations prior to enrollment in these studies were not always reported. In addition, the clinical significance of these findings is also unclear as evidence of clinical deficiency was not reported.Based on current US dietary intake of selenium that is generally higher than oral RDIs, the average patient requiring PN is not expected to be selenium-deficient at baseline.	<p>Adult and pediatric patients on PN, especially long-term PN not supplemented with selenium, may become selenium-deficient.</p> <p>Patients on PN should be supplemented with selenium.</p> <p>Routine monitoring of selenium concentrations during treatment is recommended.</p>
<u>Current Treatment Options</u>	<ul style="list-style-type: none">Selenium Injection (by American Regent, Inc.) available as selenious acid 65.4 mcg (equivalent to 40 mcg/mL elemental selenium) is a marketed, unapproved product.	<p>There is need for an approved parenteral selenium product, an essential trace element that is required to be used as a supplement for PN across all age groups. An approved product</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none">Currently, there are no FDA-approved parenteral selenium products on the market in the U.S. As the sole parenteral source, the marketed, unapproved selenious acid product has frequently been vulnerable to drug-shortages since 2012.	would help assure product quality and availability.
<u>Benefit</u>	<ul style="list-style-type: none">Unapproved marketed products may be variable in quality standards. Selenium Acid Injection demonstrated acceptable quality and manufacturing controls.Product availability for essential trace element products, such as selenium that are used across all age groups, including preterm age groups needs to be ensured to prevent drug shortage.Literature review identified 109 publications evaluating the effect of intravenous selenium supplementation on selenium concentrations in patients on chronic PN. Increase and maintenance in selenium levels were consistently observed in patients regardless of whether they were deficient at baseline.There are some inconsistencies in normal reference range for Se levels, however, routine monitoring of selenium concentrations may be useful to prevent deficiencies, especially for patients on long-term TPN.Currently, in the US, the average daily intake of selenium is estimated to be higher than RDI values and selenium deficiency is rare. RDI for selenium previously 70 mcg/day in adults was decreased to 55 mcg/day based on the 2016 Final Rule – Food Labeling: Revision of the Nutrition	<p>The collective evidence, including clinical data on selenium supplementation in PN patients, known enteral nutritional requirements (e.g., Recommended Dietary Allowance, Reference Daily Intake (RDA, RDI)), relative bioavailability of oral versus intravenous administration, current clinical PN guidelines, the available toxicity data, as well as the time and extent of use in clinical practice, is considered adequate to establish the effectiveness of Selenium Acid Injection as a source for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated</p> <p>The proposed 60 mcg/day dose for adults aligns with the oral RDI of 55 mcg/day and should be adequate for most patients. Based on clinical needs some patients may require higher doses and monitoring of selenium concentrations during treatment is recommended in the prescribing information. The label will also specify that doses can be individualized based on the patient's clinical</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>and Supplementation Facts Label.</p> <p>https://www.federalregister.gov/documents/2016/05/27/2016-11867/food-labeling-revision-of-the-nutrition-and-supplement-facts-labels</p> <ul style="list-style-type: none">• There is a range in the optimal dose that will provide a source of selenium sufficient to maintain human health. Higher selenium doses may be required to optimize function of the various selenoproteins and ensure that the reported proportion of chronic PN patients with selenium levels lower than healthy controls and below the reference range (16% to 75%) are not predisposed to selenium deficiency with suboptimal dosing.• Insufficient or inconclusive human data in special populations such as patients with burns, critical illness and pre-term neonates, who may require higher doses of selenium to achieve their dietary requirements. However, it is difficult to perform studies in such populations given their underlying clinical conditions.	<p>condition, nutritional requirements, and the contribution of oral or enteral selenium intake and that selenium levels should be monitored.</p> <p>The benefit-risk profile for Selenious Acid Injection is favorable, and any potential risks can be mitigated through product labeling.</p>
<u>Risk and Risk Management</u>	<ul style="list-style-type: none">• Adverse events associated with standard oral recommended doses of selenium as well as the proposed parenteral dose were not identified in the literature, or FAERS and CAERS databases.• Adverse events were identified with high oral doses (e.g., 200,000 mcg orally daily and 240,000 mcg orally daily) include gastrointestinal symptoms, paresthesia, alopecia, fingernail loss, and signs of thyroid deficiency that appeared to be reversible upon drug discontinuation.	<p>The short- and long-term safety profile of Selenious Acid Injection has been adequately characterized based on the published literature, human toxicity data and long-standing clinical experience.</p> <p>No serious adverse events are expected to occur with doses recommended for the proposed indication.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none">No serious adverse events were attributed to parenteral selenium in studies evaluating high intravenous doses, e.g., 2000 mcg/day, 4000 mcg/day.	<p>Routine pharmacovigilance is recommended. There are no additional risk management strategies required beyond the recommended labeling.</p> <p>PREA PMR will be issued for an age appropriate formulation to ensure accurate dosing volumes of Selenious Acid Injection for pediatric patients weighing less than 7 kg.</p>

1.4. Patient Experience Data

Patient Experience Data Relevant to This Application (check all that apply)

<input type="checkbox"/>	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
<input type="checkbox"/>	<input type="checkbox"/> Clinical outcome assessment (COA) data, such as	
	<input type="checkbox"/> Patient reported outcome (PRO)	
	<input type="checkbox"/> Observer reported outcome (ObsRO)	
	<input type="checkbox"/> Clinician reported outcome (ClinRO)	
	<input type="checkbox"/> Performance outcome (PerfO)	
	<input type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Natural history studies	
	<input type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications)	
	<input type="checkbox"/> Other: (Please specify):	
<input type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review:	
	<input type="checkbox"/> Input informed from participation in meetings with patient stakeholders	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Other: (Please specify):	
<input checked="" type="checkbox"/>	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

2.1.1. Parenteral Nutrition

Parenteral nutrition (PN), is intravenous administration of nutrition, which may include protein (amino acids), carbohydrate (dextrose), fat (lipid emulsion), minerals and electrolytes, vitamins and TEs, including selenium for patients who cannot consume or absorb enough food through oral or tube feedings to maintain an adequate nutrition status. PN may be needed for a variety of diseases or conditions that impair food intake, nutrient digestion or absorption, including premature delivery, short bowel syndrome, gastro-intestinal fistulas, bowel obstruction, critically ill patients, and severe acute pancreatitis.

PN can be used short-term or long-term in the hospital or home settings and may be used as the exclusive means to deliver nutrition or in combination with some amount of oral/enteral intake. According to the 2014 National Inpatient Survey data, over 290,000 patients received PN during their hospital stay and about 43% of those patients were newborns and children [14]. It is estimated that about 25,000 patients receive PN at home [15].

2.1.2. Selenium

TEs are essential components of complexes required for fundamental processes such as enzymatic reactions. Some TEs are well established as essential in human physiology while others' roles and requirements have yet to be defined. Selenium is an essential trace element that functions largely through an association with at least 35 selenoproteins that participate in a wide variety of biochemical functions including defense against oxidative stress, regulation of thyroid hormone, redox status of vitamin C and other molecules.

Selenium is obtained primarily through diet and the amount of selenium available in a diverse diet is typically sufficient to negate the need for additional supplementation. The precise selenium content in foods can vary greatly depending on where the produce are grown or produced. In the U.S., the estimated daily selenium intake for adults ranges between 60 and 220 mcg/day [16] and deficiency is unlikely. Deficiency in dietary selenium has been linked to certain clinical conditions, including cardiomyopathy, skeletal muscle myopathy, and nail and hair changes. As discussed further in Section 2.1.4, conditions such as cardiomyopathy have been seen historically in certain geographically Se-deficient areas worldwide, e.g., certain parts of China where the soil is Se-deficient. Also, as discussed later, Se deficiency may be associated with secondary infectious, metabolic and other stresses that may be causative.

Case reports of selenium deficient PN patients were published starting in the late 1970s and early 1980s: cardiomyopathy (1981, 1984, and 1989), skeletal muscle weakness (1979, 1986), abnormalities in nails (1983) and hair (1987) and macrocytic anemia (1987).

Interventional studies evaluating selenium supplementation in PN were published starting in the late 1980s (Lane 1987) [3].

In 1979, the Nutrition Advisory Group (NAG) of the Department of Food and Nutrition and the American Medical Association recommended that 4 TEs, zinc, copper, manganese, and chromium, be provided in adult PN formulas. In 1984, recommendations were made to add selenium (50 to 60 mcg/day) [17]. In 1994, the recommended dose range for selenium was increased (40 to 80 mcg/day) [18]. These recommendations were reviewed by the American Society for Parenteral and Enteral Nutrition (ASPEN) in 1998 [19] and 2004 [20] and a further recommendation was made to modestly decrease the dose range for selenium (20 to 60 mcg/day).

In May 2009, the A.S.P.E.N. Board of Directors formed the Novel Nutrient Task Force with a charge to assess the level of scientific evidence for the clinical use of several different parenteral nutrients and develop position statements for each nutrient. In 2012 A.S.P.E.N published a position paper based upon the 2009 task force findings, which increased the recommendations for selenium to 60 to 100 mcg/day. The position paper supports the routine addition of selenium to all PN formulas, both for adults and pediatric and neonatal PN formulas at a dose of 2 mcg/kg/day.

2.1.3. Recommended Oral Intake

The Dietary Reference Intake (DRI), developed by the Food and Nutrition Board at the Institute of Medicine (IOM) of the National Academies (formerly National Academy of Sciences) [13], is a general term used to describe a set of reference values used for planning and assessing nutrient intakes of healthy people, which can vary based on age and sex [21] and include the following:

- **Estimated Average Requirement (EAR)**: Average daily level of intake estimated to meet the requirements of 50% of healthy individuals; usually used to assess the nutrient intakes of groups of people and to plan nutritionally adequate diets for them; can also be used to assess the nutrient intakes of individuals.
- **Recommended Dietary Allowance (RDA)**: Average daily level of intake sufficient to meet the nutrient requirements of nearly all (97% to 98%) healthy individuals; often used to plan nutritionally adequate diets for individuals.
- **Tolerable Upper Intake Level (UL)**: Maximum daily intake unlikely to cause adverse health effects.

Calculation of the EAR for selenium was based on studies that determined the amount of selenium intake required to achieve maximal GSHPx activity. The IOM determined this based on results of two intervention studies, the first of which was a Chinese study [22] that demonstrated that plasma GSHPx activity plateaued at a selenium intake of 41 mcg/day. For weight adjusted North American males, the suggested daily selenium intake was 52 mcg/day. The second New Zealand study [23] reported an EAR of 38 mcg/day. Thus, the EAR for selenium

is 45 mcg/day and was chosen based on the average of these studies.

The RDA for Se was determined based on the amount needed to maximize synthesis of the selenoprotein glutathione peroxidase to cover the needs of 97 to 98 percent of the individuals in the group. The RDA for selenium is 120% of the EAR assuming a variation of 10% within the population [13]. The RDA for pediatric and adult populations ranges between 15 and 55 mcg/day (see Section 15.5) with an increased requirement during pregnancy and lactation of 60 and 70 mcg/day [13].

For estimates of adequate intake (AI) in infants ages 0 through 6 months, the RDA of 15 mcg/day or 2 mcg/kg/day is based on a mean volume of milk intake of 0.78 L/day [24-26] and an average concentration of selenium in human milk of 18 mcg/L (range 15 to 20 mcg/L) [27-30]. Using a similar method of calculation, the AI for infants ages 7 through 12 months is estimated to be 20 mcg/day or 2 mcg/kg/day.

The RDAs for children and adolescents between the ages of 1 through 18 years were extrapolated from adult values and determined to be between 20 mcg/day and 55 mcg/day [13].

The value established by the FDA for use in nutrition labeling is the RDI. The RDI is based on the highest RDA for each nutrient, to assure that needs were met for all age groups. For the purpose of nutritional labeling, 21 CFR 101.9 established the RDI of Se to be 20 mcg/day in pediatric population up to age 4; 55 mcg/day in greater than 4 years old and adults; and 70 mcg/day in pregnant and lactating females [31] (see Appendix 15.5). The RDI for selenium was previously 70 mcg/day in adults and was decreased to 55 mcg/day based on the 2016 Final Rule – Food Labeling: Revision of the Nutrition and Supplementation Facts Label.

<https://www.federalregister.gov/documents/2016/05/27/2016-11867/food-labeling-revision-of-the-nutrition-and-supplement-facts-labels>

The average amount of daily selenium intake from foods in the U.S. diet was estimated to be 111 mcg/day [32] between the years of 2015 and 2016, higher than the RDI of 55 mcg/day, implying that the average patient requiring PN should not be selenium-deficient at baseline.

2.1.4. Deficiency

Low selenium nutritional status can result from diminished selenium content in the diet, particularly in populations where foods are derived principally from livestock and vegetation grown on selenium-deficient soils (as seen in China and New Zealand), as well as in patients receiving parenteral nutrition that has not been supplemented with selenium [33-35]. In addition, deficiencies may occur due to inappropriate administration of micronutrients during nutrition therapy or because of increased requirements or increased bodily losses [36]. Selenium was established as an essential TE for humans in 1979, when Chinese scientists demonstrated improvement in children with Keshan disease [37] after selenium

supplementation. Keshan disease was first described in 1935 in Northeast China in the setting of sudden onset cardiogenic shock, cardiomegaly, congestive heart failure and arrhythmias in children 2 to 7 years old and women of child-bearing age [38]. Subsequent epidemiology studies revealed that the occurrence of Keshan disease was endemic and was associated with selenium deficiency and seen primarily in certain parts of China where the soil is severely selenium-deficient [39]. Similarly, Kashin-Beck disease, a chronic, endemic osteochondropathy also seen primarily in certain areas of China has also been linked to selenium deficiency [40]. For Keshan disease, it appears that additional stresses such as infection (e.g., coxsackievirus B3[41]) or chemical exposure in the setting of selenium deficiency may trigger cardiomyopathy. Whereas for Kashin-Beck disease, selenium supplementation has not appeared to prevent the disease, suggesting that deficiency of selenium may not be the dominant cause. Additionally, while clinical thyroid disorders have not been reported in selenium deficiency, it is possible that patients who have both selenium and iodine deficiency may be at increased risk of cretinism.

Clinical signs and symptoms associated with selenium deficiency have been reported to include cardiomyopathy [34, 42], skeletal myopathy, muscle weakness, macrocytosis, whitened nailbeds, and loss of pigmentation of hair and skin. In infants on chronic TPN, alopecia and growth retardation have been reported in selenium deficient patients [43]. While signs and symptoms of deficiency are generally associated with very low plasma Se levels (e.g., <2 mcg/dL), the relationship between symptom onset, severity and Se levels is unclear since very low Se levels have been seen in patients without overt clinical manifestations [44, 45]. While case reports of patients with selenium deficiency suggest that some clinical signs and symptoms are reversible with selenium supplementation (Appendix 15.10 and 15.12), optimal dosing to treat clinical deficiency has not been established and is likely to be based on a patient's clinical needs. As discussed later, notwithstanding challenges associated with Se levels, monitoring Se levels, especially in patients on long-term PN, may prevent deficiency.

2.2. Analysis of Current Treatment Options

Other parenteral formulations of selenious acid have been available in the US as marketed unapproved products for many years.

- Selenium Injection (65.4 mcg/mL selenious acid equivalent to 40 mcg/mL selenium), available in 10-mL and 30-mL vials has been marketed since 1990 as an additive to PN.
- Multitrace-5 (MTE-5) (20 mcg/mL selenium in a 10-mL multidose vial) and MTE-5 concentrate (60 mcg/mL selenium in a 1-mL single-dose vial and 10-mL multidose vial). This is a fixed-combination product containing 5 trace elements (chromic chloride, cupric sulfate, manganese sulfate, selenious acid, and zinc sulfate heptahydrate).

Both products are manufactured by American Regent.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Selenious Acid Injection is a new chemical entity (NCE). See Section 2.2 Analysis of Current Treatment Options regarding marketed, unapproved selenious acid parenteral products.

As a sole source product, the marketed unapproved intravenous selenium acid products are vulnerable to drug shortage and have frequented the drug-shortage list since 2012.

3.2. Summary of Presubmission/Submission Regulatory Activity

Since 2009, ASPEN has been in communication with the Division of Gastroenterology and Inborn Errors Products on multiple occasions due to concerns relating to lack of approved parenteral nutrition products, drug shortages and marketed unapproved products. ASPEN has urged the Agency to approve safe and effective injectable TE products (including selenium) that comply with the current standards of clinical practice, fulfill the Agency's quality standards, and meet the supply and demand of the market.



(b) (4)

The Applicant submitted the marketing application for Selenium Acid Injection intended for use in PN (NDA 209379) on October 31, 2018, under a literature-based 505(b)(2) New Drug Application (NDA) pathway. The application is classified as a Priority Review due to drug-shortage issues with an Action Date of April 30, 2019.

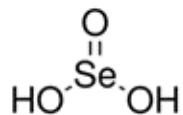
4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI audit was not requested or performed given that the Applicant did not conduct any clinical trials.

4.2. Product Quality

The active ingredient, selenious acid, USP is a colorless, white crystalline, hygroscopic powder with characteristic acid odor. It is soluble in water and freely soluble in alcohol. Its empirical formula is H_2SeO_3 and its molecular weight is 128.97 g/mol. The structural formula of selenious acid is as follows:



Selenious acid, USP is manufactured by [REDACTED] (b) (4). The overall quality of Selenious acid, USP is controlled by its specification. The drug substance manufacturing process, specification and stability data were deemed adequate per drug substance reviewer. The particle size and polymorphs of selenious acid are not important because the drug product is an injection. The API is controlled to conform to the requirements (specification) to produce Selenious Acid Injection, USP.

Selenious Acid Injection, USP, 60 mcg/mL sterile, non-pyrogenic, clear, colorless solution for intravenous use, is supplied in 10 mL glass vials. Each mL of the solution contains 60 mcg of selenium as 98 mcg of selenious acid in water. The pH of the solution is adjusted to 1.8 to 2.4 with nitric acid. The drug product does not contain any preservatives or antioxidants.

The drug product is manufactured by American Regent, Inc., NY, using [REDACTED] (b) (4)

(b) (4) The drug product manufacturing process and microbiology related sections were reviewed and deemed adequate for manufacturing process robustness and sterility assurance.

The Applicant provided data to demonstrate that potential leachables including (b) (4) are below daily dose permitted daily exposures (PDEs). The scanning electron microscope testing demonstrated the vials did not exhibit peeling or delamination of glass. In addition, the admixture study indicated that Selenious Acid Injection, USP is compatible with Kabiven and Clinimix E parenteral nutrition solutions.

The overall control strategy for the drug product's identity, strength, purity and quality was deemed adequate.

A claim of categorical exclusion from the requirements of an environmental assessment in accordance with 21 CFR Part 25.31 was deemed acceptable.

The CMC sections of the labeling/labels are acceptable.

This NDA is recommended for approval from the OPQ perspective.

4.3. Clinical Microbiology

The environmental monitoring at (b) (4) manufacturing process (b) (4), (b) (4) as well as the microbiology related attributes of the drug product specification including bacterial endotoxins, sterility and container closure integrity etc. were reviewed by Dr. Samata Tiwari and recommended for NDA approval based on drug product sterility assurance (See Microbiology Review in the OPQ IQA).

4.4. Devices and Companion Diagnostic Issues

No companion device or diagnostic was included in this NDA.

5. Nonclinical Pharmacology/Toxicology

5.1. Nonclinical Executive Summary

No nonclinical studies have been conducted by the Applicant with Selenious Acid Injection, and the Applicant is relying on published literature to support marketing approval.

Limited data from published literature exists to assess the toxicity of intravenously administered selenious acid or selenium. Selenium absorption in animals is dependent on the salt form of the selenium-containing compound, but selenium is mostly absorbed through the small intestine. Following its absorption, selenium distributes throughout the body, but primarily to the liver, kidney, lung, and muscle tissue. Selenious acid is the acid form of sodium selenite, the inorganic source of selenium, that dissociates into its component ions in the gastrointestinal tract. Selenium dissociated from sodium selenite is metabolized into hydrogen selenide and dimethyl selenide by reduction and methylation reactions requiring glutathione and nicotinamide adenine dinucleotide phosphate (NADPH). Selenium is primarily excreted via urine, followed by feces and expired air.

No toxicology data exist with intravenously administered selenious acid or selenium containing compounds. In subchronic and chronic toxicity studies where rodents were orally administered sodium selenite, the liver was the major target organ of selenium toxicity, followed by the immune system (innate and humoral). The mutagenicity of selenium is equivocal, based on conflicting results from in vitro and in vivo assays. The carcinogenic and reproductive and developmental toxicity potential of selenium and selenium containing compounds cannot be definitely determined due to conflicting results in several animal studies.

The Applicant conducted a risk assessment of all Class 1, 2A, 2B, and 3 elemental impurities recommended in ICH Q3D, as well as [REDACTED]^{(b) (4)}. An extractables/leachables assessment was also conducted. There are no safety concerns for elemental impurities or identified leachables in the drug product container closure system.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Selenium, as a component of glutathione peroxidase, protects cell components from oxidative damage by catalyzing peroxides produced by cellular metabolism [46].

5.4. ADME/PK

Table 1: Summary of ADME/PK Studies and Major Findings

Type of Study	Major Findings
Absorption	
[47] EFSA Journal (2009) 1009, 9-17	90% oral absorption of sodium selenite in rats, 40 to 70% oral absorption in humans
Distribution	
[48] NTP 1994	Primarily to liver, kidneys, lung, and muscle tissue
Metabolism	

Type of Study	Major Findings
[48] NTP 1994; [47] EFSA Journal (2009) 1009, 9-17	Selenium dissociated from sodium selenite metabolized into hydrogen selenide and dimethyl selenide by reduction and methylation reactions requiring glutathione and NADPH
Excretion	
[48] NTP 1994	Primarily excreted via urine, followed by feces and expired air

Abbreviations: NADPH = nicotinamide adenine dinucleotide phosphate

5.5. Toxicology

5.5.1. General Toxicology

Selenious acid is the acid form of sodium selenite, the inorganic source of selenium, that dissociates into its component ions in the gastrointestinal tract. The toxicity of selenium varies according to the valence state when incorporated into biomolecules and by the route of intake or administration [46, 49]. No studies have assessed the toxicity of Selenious Acid Injection or intravenously administered selenium or selenious acid. However, the toxicity of orally administered sodium selenite has been well established and is used to inform the potential toxicity of intravenously administered selenious acid. The liver is the major target organ of selenium toxicity, followed by the immune system (innate and humoral).

Reduced body weight gain, increased spleen weight, and liver lesions including hobnailed/pebbled appearance and severe cirrhosis and necrosis were observed in Holtzman rats administered 0.25 mg Se/kg/day (sodium selenite) in the diet for 6 weeks [46].

Reduced body weight gain and histopathological findings in the liver (periportal: oval cell proliferation and pigment accumulation in macrophages; centrilobular: hepatocellular hypertrophy, enlargement of hepatocyte nuclei, focal and single-cell necrosis) were observed in Syrian hamsters administered 1.21 mg Se/kg/day (sodium selenite) in the diet for 6 weeks. No adverse effects were observed at 0.61 mg Se/kg/day [46].

Focal coagulation hepatocellular necrosis was observed in rats administered 31.6 mg Se/kg/day (selenium sulfide) via oral gavage for 13 weeks. This finding was not observed at 17.8 mg Se/kg/day [46].

Reduced humoral antibody (IgC) production, prostaglandin synthesis, and increased natural killer cell cytotoxicity were observed in rats administered 0.75 mg Se/kg/day via drinking water for 10 weeks. Increased natural killer cell cytotoxicity was also observed at 0.28 mg/kg/day [46].

In a toxicity study in which female Long-Evans rats were administered sodium selenite via drinking water for 24 months (104 weeks), survival, body weight, and heart weights were decreased in females administered 0.173 mg Se/kg/day. 49% of the animals in this dose group died at \leq 9 months of age with atrophied and fatty livers. In one 0.173 mg Se/kg/day female that survived until termination, focal cirrhosis of the liver was observed. No other organs were affected [46].

Decreased physical activity and increased amyloidosis of the kidney, heart, adrenal, liver, spleen, and lung were observed in Charles River CD mice administered 0.56 mg Se/kg/day (sodium selenite) via drinking water for their entire lifetime (duration not specified) [46].

5.5.2. Genetic Toxicology

The available mutagenicity data for selenium and selenium containing compounds are equivocal [47, 50]. In published literature, selenium is both mutagenic and anti-mutagenic in *in vitro* assays, though in the majority of *in vivo* studies, selenium compounds are anti-mutagenic [47]. These challenges preclude an accurate determination of the mutagenic potential of Selenious Acid Injection.

5.5.3. Carcinogenicity

Though the carcinogenic potential of orally administered selenium and selenium containing compounds have been evaluated in several published studies, the data are conflicting due to the various salt forms of selenium used in the studies and, thus, difficult to compare [50]. For example, while orally administered sodium selenite and sodium selenate are not considered to be carcinogenic in rats or mice, hepatocellular carcinomas in mice and rats have been associated with oral administration of selenium sulfide, selenium disulfide, and selenium monosulfide. Alveolar/bronchiolar carcinomas and adenomas in mice have also been associated with orally administered selenium sulfide [46]. These challenges preclude an accurate determination of the carcinogenic potential of Selenious Acid Injection [50].

5.5.4. Reproductive and Developmental Toxicology

Though the reproductive and developmental toxicity of orally administered selenium containing compounds has been evaluated in several studies, the data are difficult to compare due to the differences in effects with the various salt forms and animal models used in the studies. In cattle, sheep, and horses fed selenium (20 to 50 mg/kg) in the diet, decreased rates of conception and increased fetal resorption have been observed [46]. In long-tail macaques, no maternal or fetal developmental effects or adverse developmental outcomes were observed after daily oral administration of selenomethionine (up to 300 mcg Se/kg/day) from gestational day 20 to 50 [50]. In post-weanling male rats, growth reduction was observed after daily oral administration of sodium selenite or seleniferous wheat (40 to 94 mcg Se/kg/day) for 6 weeks. In mice fed sodium selenite (390 mcg/kg/day) through four generations, deaths in the F1 generation, decreased breeding in the F3 generation, and an increased number of runts in the F1-F3 generation were observed [50]. Conversely, in mice administered sodium selenite (390 or 780 mcg/kg/day) 30 days prior to mating and throughout gestational day 18, no treatment-related effects were noted on the embryos and/or fetuses [50]. Orally administered sodium selenate had no effect on reproduction in a 3-generation study in mice [46]. These challenges

preclude an accurate determination of the reproductive and developmental toxicity of Selenious Acid Injection.

5.5.5. Other Toxicology Studies

Safety Assessment of Elemental Impurities

The Applicant conducted a risk assessment of all Class 1, 2A, 2B, and 3 elemental impurities recommended in ICH Q3D. A risk assessment was also conducted for [REDACTED] (b) (4) aluminum [REDACTED] (b) (4). The Applicant's specifications for elemental impurities are below the ICH Q3D recommendations. The Applicant also adequately determined the specification limits of [REDACTED] (b) (4) aluminum. The measured amounts of all elemental impurities were below their specification limits and, therefore, there are no safety concerns for elemental impurities. Overall, the elemental impurity profile associated with the drug product container closure system appears to be acceptable.

(b) (4)

The calculation of the PDE for [REDACTED] (b) (4) was based on the no-observed-adverse-effect level (NOAEL) of [REDACTED] (b) (4) mg [REDACTED] (b) (4) /kg/day determined in an oral embryofetal developmental toxicity study in rabbits, as reported in the Agency for Toxic Substances and Disease Registry for [REDACTED] (b) (4) [51], the bioavailability of [REDACTED] (b) (4) is 93.9% in humans and 95% in animals (rats). The calculated PDE of [REDACTED] (b) (4) mg/kg/day (shown below) is much higher than the specification limit set for [REDACTED] (b) (4) (b) (4) mcg/mL; [REDACTED] (b) (4) mcg/day). Therefore, the Applicant's specification for [REDACTED] (b) (4) is acceptable.

PDE [REDACTED] (b) (4)

F1= [REDACTED] (b) (4) (rabbit to human)
F2= [REDACTED] (b) (4) (individual variability)
F3= [REDACTED] (b) (4) (reproductive study)
F4= [REDACTED] (b) (4) (fetal teratogenicity with no maternal toxicity)
F5= [REDACTED] (b) (4) (NOAEL was used)
F6= [REDACTED] (b) (4) (50 and <90% bioavailability)

(b) (4)
The tolerable upper intake levels (UL) of oral [REDACTED] (b) (4) for infants 0 to 6 months of age is [REDACTED] (b) (4) mg/day [52]. The recommended UL of [REDACTED] (b) (4) in infants is 20,000x higher than the Applicant's specification limit ([REDACTED] (b) (4) mcg/mL; [REDACTED] (b) (4) mcg/day). Thus, the Applicant's specification for [REDACTED] (b) (4) is acceptable.

(b) (4)
The RDA and AI of [REDACTED] (b) (4) in pediatric patients is [REDACTED] (b) (4) mg/day ([REDACTED] (b) (4) mcg/day) [53]. The RDA and AI of [REDACTED] (b) (4) is 60 to 1500x higher than the specification ([REDACTED] (b) (4) mcg/mL; [REDACTED] (b) (4) mcg/day). Thus, the Applicant's specification for [REDACTED] (b) (4) is acceptable.

(b) (4)

The calculation for the PDE of (b) (4) is based on the NOAEL of (b) (4) mg/kg/day determined in a 3-month toxicity study in rats administered (b) (4) via drinking water, as reported in the Organization for Economic Co-operation and Development (OECD) Screening Information DataSet (SIDS) on (b) (4) [54]. The bioavailability of (b) (4) is unknown, so an uncertainty factor of 10 was applied. The calculated PDE of (b) (4) mg/kg/day (shown below) is much higher than the specification limit set for (b) (4) (b) (4) mcg/mL; (b) (4) mcg/day). Therefore, the Applicant's specification for (b) (4) is acceptable.

PDE = (b) (4) (b) (4)

- F1 (b) (4) (rat to human)
- F2 (b) (4) (individual variability)
- F3 3-month study in rodents)
- F4 no severe toxicity)
- F5 NOAEL was used)
- F6 (b) (4) (bioavailability unknown)

Safety Assessment of Aluminum

The Applicant's aluminum specification of (b) (4) mcg/L is acceptable for pediatric patients <10 kg, including preterm neonates weighing 0.5 kg, based on a maximum daily dose of 7 mcg/kg Selenious Acid Injection and concentration of 60 mcg/mL. At this specification, the daily patient exposure to aluminum will be <0.6 mcg/kg/day ((b) (4) mcg/kg/day). As this is a small volume parenteral intended for use in a multi-component PN, this specification and daily exposure limit of aluminum should ensure the daily patient exposure from all potential sources of aluminum in the TPN admixture does not exceed 5 mcg/kg/day (21 CFR 201.323).

Safety Assessment of Extractables/Leachables

The known extractables from the 10 mL (b) (4) USP Tubular 20 mm (b) (4) Vial ((b) (4) .) and 20 mm (b) (4) stopper (b) (4) are (b) (4) .

The Applicant conducted leachables assessments using the reverse-phase high performance liquid chromatography-diode array detection (HPLC-DAD) method and Total Organic Carbon (TOC) method on upright samples and inverted samples to represent the *worst-case* scenario due to product contact with the stopper. For both methods, samples were stored at 40°C/75% relative humidity (RH) and 25°C/60% RH for 6 months. Additionally, with the TOC method, samples were also stored at 25°C/60% RH for 27 months. Three organic leachables were detected, with total daily intakes of less than or equal to (b) (4) mcg/day. No additional leachables were detected in the inverted samples compared to the upright samples, suggesting no leachables from the stopper ((b) (4) .) were detected. As these leachables were detected at levels lower than the Product Quality Research Institute qualification threshold for mutagens/carcinogens in parenteral products (1.5 mcg/day), there is

no safety concern for the identified leachables. Overall, the leachable profile associated with the drug product container closure system appears to be acceptable.

6. Clinical Pharmacology

6.1. Clinical Pharmacology Executive Summary

Selenium is an essential trace element incorporated into enzymes known as selenoproteins as selenocysteine. Selenoproteins include but are not limited to, glutathione peroxidase, iodothyronine deiodinase, peroxidase and thioredoxins. Selenious acid is the acid form of sodium selenite, the inorganic source of selenium, that dissociates into its component ions in the body. The Applicant proposed Selenious Acid Injection for intravenous administration in adult and pediatric patients as a source of selenium for PN when oral or enteral nutrition is not possible, insufficient, or contraindicated. Selenious acid should be admixed with parenteral nutrition solution prior to administration and infused per TPN infusion rate.

The Applicant proposes to rely on safety and efficacy of the proposed product solely on published literature and case reports, and no clinical trials were conducted for the proposed product by the Applicant.

6.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed this submission and found it acceptable for approval from a clinical pharmacology standpoint.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacology

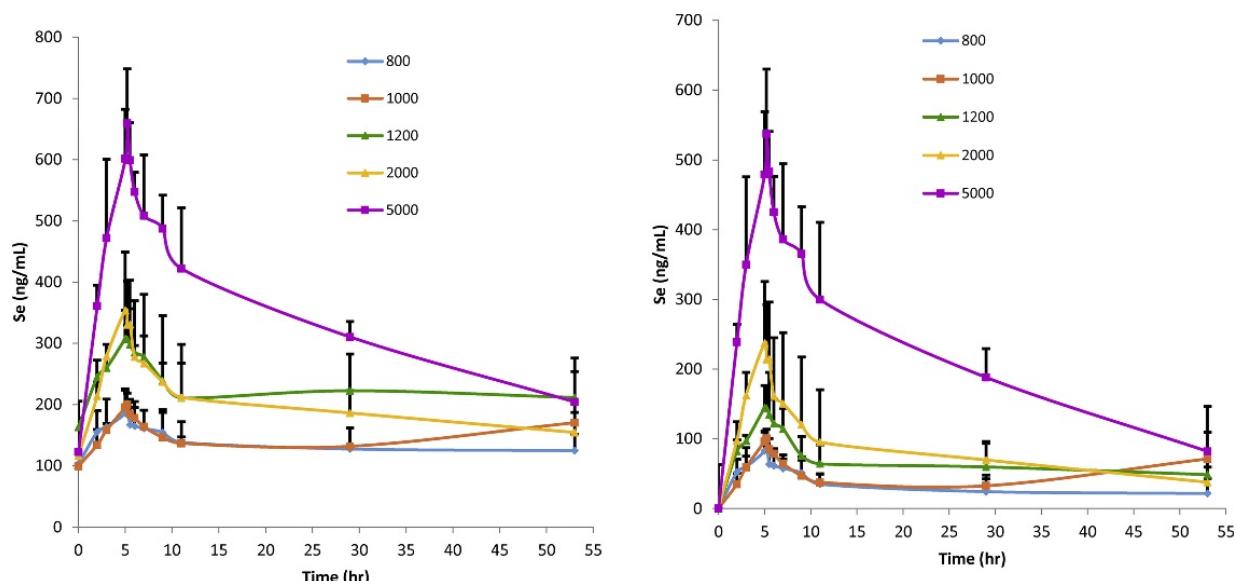
Selenium is an essential trace element and incorporated into selenoproteins as selenocysteine, the selenium analogue of cysteine, in which selenium replaces sulfur. Selenoproteins include but not limited to, glutathione peroxidase, iodothyronine deiodinase, peroxidase and thioredoxins. The known biological functions of selenium include defense against oxidative stress, regulation of thyroid hormone action, and regulation of the redox status of vitamin C and other molecules [55]. Selenious acid (H_2SeO_3) is reduced to hydrogen selenide(H_2Se) via glutathione-involved electron reductions in red blood cells and is a precursor for the synthesis of selenoproteins.

Clinical Pharmacokinetics

While periodic monitoring of selenium concentrations during long-term PN at varying doses has been reported, the full pharmacokinetic (PK) characterization of selenium following intravenous administration of selenious acid to patients on parenteral nutrition is not available.

On the other hand, full PK of total selenium in plasma was reported by Song et al. [56]. following a single dose administration of selenious acid (American Regent) infused over 5 hours at doses ranging from 50 to 5000 mcg in chemo-naïve female cancer patients who were not on parenteral nutrition. At baseline, plasma Se concentrations in these patients (n=45) ranged from 7.6 to 14.1 mcg/dL with a mean Se concentration of 11.6 mcg/dL, which was in ranges similar to that observed in the general population [57]. PK parameters were not reported at doses 50, 100, 200 and 400 mcg because plasma Se concentrations at these doses fluctuated near the baseline selenium concentrations and PK analyses could not be done. However, a dose-dependent increase in the systemic exposure of total blood selenium was observed at doses from 800 mcg to 5000 mcg following intravenous infusion of selenious acid over 5 hours [56]. After correction for baseline Se concentration, C_{max} at the end of infusion increased from 10.1 to 53.7 mcg/dL, and AUC of plasma selenium increased from 256.2 to 1095 mcg/L*h with the dose increase from 800 to 5000 mcg/day. The half-life of selenium ranged 8.2 to 74.4 h with mean half-life of 25 h.

Figure 1: Plasma Selenium Concentration-Time Profile, by Dose Cohort, Without Baseline Correction (Left) and With Baseline Concentration Subtracted (Right)



Note: Plasma elemental selenium concentration after single dose administration of selenious acid intravenously infused over 5 hours in female cancer patients in different dose cohorts (n = 5; 800 mcg), (n = 3; 1000 mcg), (n = 5; 1200 mcg), (n = 3; 2000 mcg); (n = 4; 5000 mcg).

Oral Bioavailability

To estimate the intravenous dose based on the recommended oral daily intake for selenium, the oral bioavailability of enteral selenium supplementation was considered. In diets, selenium exists in both inorganic (selenite and selenate) and organic (selenomethionine and selenocysteine) forms, and the recommended oral daily intake does not differentiate the selenium form, however, may be supplied by any selenium form. Oral absorption apparently varies depending on the selenium form. Ideally a study with the isotope labelled selenium

could have provided more accurate oral bioavailability. Because the oral selenium intake was mostly estimated based on the selenium content in diet over time in balance studies and endogenous selenium was present, the reported oral bioavailability from balance studies is considered semi-quantitative.

Nevertheless, studies in humans suggest that selenite is less readily absorbed than selenate and organic selenium. For example, the absorption of an oral 10 mcg dose of ^{75}Se labelled selenite ranged from 44 to 70% in three human volunteers [58]. Analysis of 72-hour urine samples from a study in which 48 Norwegian women were given a 200 mcg supplement of selenium in the form of selenite or selenium-rich pea flour indicated approximately 50% absorption of selenite [59]. On the other hand, organic forms of selenium such as selenomethionine were reported to be highly bioavailable (>90%), and selenocysteine appears to be almost 100% absorbed per the reports of the U.S. Food and Nutrition Board [60]. Bioavailability of selenium in humans using stable isotope labelled selenium showed that apparent absorption ranged from 54%, to 90% for the selenium from the three test meals (yeast powder, cooked or salted fish) compared to the 93% from sodium selenate in water [61].

In summary, considering all the available data, the oral bioavailability of selenium from oral supplementation is estimated to range from 44 to >90%.

There is no head-to-head comparison between the effects of oral selenium and iv selenium on plasma selenium concentrations; however, published studies suggested that plasma selenium concentrations after administration of intravenous selenium in home TPN patients compared to oral selenium in healthy subjects at similar selenium doses were similar. In healthy subjects, after oral intake of selenium (sodium selenite and L-selenomethionine) at 66 mcg selenium dose daily for 20 weeks, the mean plasma Se concentration was about 9 mcg/dL [62]. On the other hand, when 69.14 mcg of selenium was administered via intravenous infusion over 1 year in home TPN patients, the mean plasma Se concentrations were 9.87 mcg/dL [63]. The Se plasma concentrations were within the reference range in healthy subjects or TPN patients in these studies. The plasma Se concentrations in home TPN patients receiving intravenous selenium over 1 year appear to suggest no significant accumulation after multiple doses while Se concentrations similar to baseline Se concentrations were noted in female cancer patients after single dose administration of 50 to 200 mcg (ranged from 7.6 to 14.1 mcg/dL with a mean Se concentration of 11.6 mcg/dL) by Song et al. [56].

Distribution

85% of intravenously administered ^{75}Se is protein-bound within 4 to 6 h and 95% by 24 h. [58, 64].

Metabolism

Selenious acid is reduced to hydrogen selenide in red blood cells via reduction reactions requiring glutathione and hydrogen selenide is a precursor to form selenoproteins. Prior to incorporation into essential selenoproteins, selenium from both inorganic sources and organic sources, is converted to hydrogen selenide [65, 66]. Hydrogen selenide that is surplus to

requirements is further metabolized to methylated derivatives or selenosugars and excreted in urine or oxidized to selenium dioxide.

Excretion

Selenium is eliminated primarily in urine [67]. Rij et.al, reported 15% to 50% selenium excretion in urine with parenteral treatment of selenium (Semet-Se or selenious acid) in four male patients [68]. Smaller amounts of selenium are eliminated in the feces after both oral and parenteral administration. Ancillary routes of elimination are lungs and skin.

Range of Plasma Selenium Concentration for TPN Patients

Assessment of the selenium status is possible by determination of the selenium concentration in serum/plasma, whole blood, erythrocytes and urine. Plasma concentration of selenium can reflect short-term changes in the selenium balance during supplementation of selenium, however, the relationship between the systemic selenium concentrations and selenium amount in tissues has not been well established in humans.

The ranges in healthy adult subjects across publications generally overlap from 4 to 16 mcg/dL although varied across different published studies. The variability in the reference range may be related to heterogeneity of the studied populations (e.g. geographic location), various sample preparation methods, insensitive or inconsistent analytical settings and different bioanalytical assay methods. Refer to Appendix 15.6 for Reference Range of Selenium Assays in Literatures.

6.2.2. General Dosing and Therapeutic Individualization

Applicant's Proposed Dosing

The Applicant proposed dosing schedule based on amount of elemental Se is shown in Table 2.

Table 2: Applicant Proposed Dosing

		Dosing for Selenious Acid Injection (60 mcg/ml of elemental Se)
(b) (4)	kg	2 to 4 mcg/kg/day
(b) (4)	kg to	(b) (4) mcg/day
(b) (4)		60 mcg/day

General Dosing in Adults

As a source of selenium, the proposed dose of 60 mcg is acceptable. The proposed intravenous (IV) dose, 60 micrograms of selenium, is close to the Reference Daily Intake (RDI) from diet, i.e., 55 mcg/day, and is partly consistent with the ASPEN guideline of 60 to 100 mcg/day.

The oral bioavailability of enteral selenium supplementation can significantly vary depending on the selenium form in humans and is estimated from 44% to >90% to precisely translate the oral selenium dose to intravenous selenium dose as a source of selenium while the proposed intravenous selenium dose is higher than the RDI even when 100% oral bioavailability is assumed.

Although the proposed dose is higher than RDI (60 mcg/day vs. 55 mcg/day), a slightly higher intravenous dose does not pose any significant safety issues given similarly maintained plasma selenium concentrations in home TPN patients based on the published studies for intravenous selenium at 69.14 mcg/day in home TPN patients and oral selenium at 66 mcg/day in healthy subjects.

However, published studies also indicated that doses higher than 60 mcg/day may be needed for some patients based on the suboptimal maintenance of selenium concentrations at doses 63 mcg/day and 85 mcg/day. Suboptimal maintenance of selenium concentrations at doses 63 mcg/day (33% patients showed micronutrient deficiency) and 85 mcg/day (25% patients showed need for higher selenium doses) in published reports [69, 70]. The selenious acid dose may be further individualized to meet patient's needs. Nevertheless, the published studies are limited to establish a dose-response relationship and to clarify the clinical conditions that necessitate higher doses. Therefore, periodic monitoring of plasma/serum selenium levels will be useful to monitor whether parenteral selenium supplementation is sufficient for a given patient.

Pediatrics

The revised proposed dosing to 2 to 4 mcg/kg/day in

(b) (4) pediatric population <7 kg
(b) (4) is acceptable. (b) (4)

Furthermore, the Applicant recognizes that additional selenium supplementation can be added to meet a patient's changing needs.

Therapeutic Individualization

Renal Impairment

Selenium is primarily excreted via the kidney. There are no publications that report effects of renal impairment on the excretion of selenium following administration of exogenous selenium. Nevertheless, Shiu et al. [72] reported that selenium concentrations in adult patients with chronic kidney disease (CKD) stages 1 to 4 who were not on TPN Selenium is primarily excreted via the kidney. There are no publications that report effects of renal impairment on the excretion of selenium following administration of exogenous selenium. Nevertheless, Shiu et al. [72] reported that selenium concentrations in adult patients with chronic kidney disease (CKD) stages 1 to 4 who were not on TPN were not significantly different by disease stage suggesting no significant accumulation of selenium in patient with renal impairment:

Table 3: Selenium Concentrations in Patients with Chronic Kidney Disease Stages 1 through 4

Stage of Chronic Kidney Disease	Estimated Glomerular Filtration Rate	Serum Selenium Concentrations (mcg/dL)
Stage 1	≥90 mL/min/1.73 m ²	14.6±2.0
Stage 2	60-89 mL/min/1.73 m ²	14.4±2.3
Stage 3	30-59 mL/min/1.73 m ²	14.1±2.3
Stage 4	15-29 mL/min/1.73 m ²	14.5±1.8

Similarly, Esmaeili et al. (2019) [73] demonstrated that no significant difference in the Se concentrations between patients with CKD not on dialysis (11.8±2.2 mcg/dL) and healthy controls (11.5±2.5 mcg/dL) in a cross-sectional, case-control study in children with CKD (N=122). In the same study, [73], the mean serum Se in hemodialysis (HD) (10.2±1.6 mcg/dL) and peritoneal dialysis group (10.0±1.2 mcg/dL) were lower compared to patients with CKD not on dialysis and healthy controls.

Based on the available data in patients with CKD, at the proposed dose for a nutrient source of selenium, no dosage adjustment for renal impairment seems to be warranted [74]. Patients on hemodialysis may need higher doses of selenious acid due to increased selenium excretion via dialysis. However, the reported Se concentrations in patients on HD were generally within the normal range and the long-term consequences of no/low selenium supplementation for patients on HD are unclear.

Outstanding Issues

There are no outstanding issues that would preclude the approval of Selenious Acid Injection from a clinical pharmacology perspective.

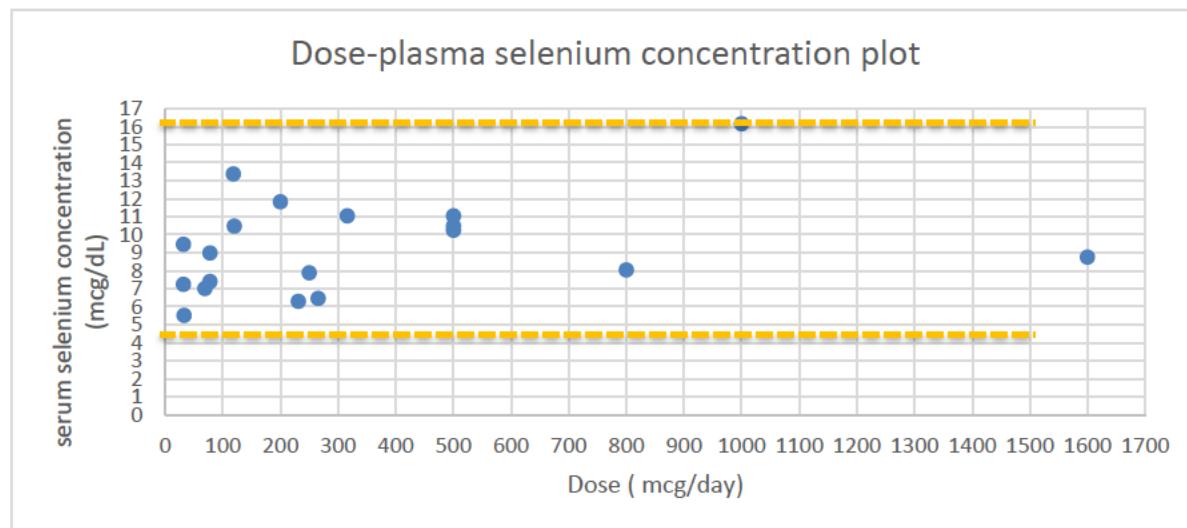
6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The submitted literature for parenteral selenium, were reviewed and categorized as follows: home TPN studies including 9 controlled studies, 11 uncontrolled studies and 12 case summaries; and studies in critically ill patients including 16 controlled studies. Refer to the list of relevant clinical trials in Appendix 15.13. The plasma selenium concentrations at last visit (C_{trough}) from the various studies (N=14) were compiled in Figure 2 to correlate with intravenous injection dose (Appendix 15.6).

There was no clear correlation between the daily dose of selenium via intravenously (e.g. sodium selenite) administration and plasma Se concentrations in patients on long-term home TPN or critically ill patients with higher dosage (125-1600 mcg/day) of selenium (see Table 15 in Appendix 15.6). Although the comparison of single timepoint plasma concentration across studies is limited, plasma Se concentrations were generally within the range (4.6 to 16.5 mcg/dL) across doses from 32 to 1600 mcg/day.

Figure 2: Dose and Plasma Selenium Concentration Correlation Plotting



6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The proposed product is a nutrient selenium source in patients on TPN and the submission is solely relying on published literatures. There are no clinical pharmacology programs submitted, but the review of literatures supported drug effectiveness under proposed dose regimen.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed adult 60 mcg/day dosage is appropriate but the dose regimen for pediatrics needs to be revised. See Section 8.4 for Clinical Efficacy for detailed discussion.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Dosage adjustment for mild to severe renal impairment is not necessary. If patients with comorbid renal impairment have greater nutritional needs, higher doses may be appropriate. See Section 8.1.5 for Clinical Efficacy for detailed discussion.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Based on a review of the 72 publications (58 in adults and 14 in pediatric populations) submitted by the Applicant, there were 2 non-randomized, controlled studies in adults and 2 randomized, controlled studies in neonates representing the best evidence to support the proposed indication of source of selenium for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. These studies are briefly outlined in Table 4 and Table 5 and discussed in greater detail in the following efficacy sections. The remaining observational and case summaries are briefly summarized in Appendix 15.9 with complete details available in Module 2.5 of the NDA and full references available in Module 5.4.

Table 4: Listing of Clinical Trials Relevant to NDA 209,379 (Adults)

First Author, Year, Location	Study Objective	Patient Population, Number of Patients	Dose of Selenium IV and Duration	Reported Findings	Comments Relevant to the Proposed Indication
Lane et al. 1987 [3] U.S.	Determine the effect of parenteral selenium (as selenious acid) on the selenium status of patients with malabsorption on long-term TPN (>1 year).	Adult patients on TPN \geq 12 months: • TPN: 7 ○ Mean age: 44 years (Range 31 to 52) • Healthy controls: 26 ○ Mean age: 37.2 years (Range 29 to 49)	Se in TPN: 0, 80, 160 mcg/day; each for 1 month Healthy controls (estimated dietary oral Se of 50 to 200 mcg/day)	<ul style="list-style-type: none"> Mean plasma Se was low compared to controls at all 3 doses but was the lowest when patients received no supplement Se 80 mcg/day: mean plasma Se was 28% of the mean control level Se 160 mcg/day: mean plasma Se was 58% of the mean control level 	<ul style="list-style-type: none"> Authors did not comment on whether clinical symptoms of Se deficiency were assessed at baseline and throughout the study period. Baseline Se supplement status and levels were not reported, therefore it is unclear if patients were biochemically deficient at the beginning of clinical trial. Se supplementation led to dose-dependent increased Se and GSHPx levels in patients but were still below the mean values of healthy controls. Urinary selenium increased with increasing exogenous selenium.

First Author, Year, Location	Study Objective	Patient Population, Number of Patients	Dose of Selenium IV and Duration	Reported Findings	Comments Relevant to the Proposed Indication
Sando et al. 1992 [4] Japan	To evaluate the effect of parenteral Se on various Se levels in long-term TPN patients.	Patients with chronic GI disease on LT TPN (mean 74.7 months; range 37 to 156 months) TPN: N=6 Mean age: 25.8 years (Range 4 to 38 years) Healthy controls: N=26 Mean ag: 29 years (Range 22 to 40 years)	Adults: 200 mcg/day Children: 7 to 10 mcg/kg/day 3-part study: 1. Se supplement x 127 weeks 2. Se was then withdrawn for 12 weeks 3. Se supplement recommended after 12 weeks	<ul style="list-style-type: none"> RR established based on healthy controls All Se indices at the end of Part-1 were within the RR Plasma Se decreased with Se withdrawal and then increased again when supplementation resumed Platelet GSHPx activity was the most sensitive index of Se status in TPN patients Erythrocyte Se indices showed no significant changes during the study period 	<ul style="list-style-type: none"> Note the mixed adult and pediatric population. Authors did not provide a rationale for the dose selection or specify if patients received selenium supplementation prior to enrollment of the study. Study was conducted in Japan and applicability of study results to a U.S. population is unclear. Patients can be considered to serve as their own controls. No clinical signs and symptoms suggestive of Se deficiency or toxicity were observed throughout the study period.

Abbreviations: F = female; GI = gastrointestinal; GSHPx = glutathione peroxidase; Hgb = hemoglobin; HPN = home parenteral nutrition; IV = intravenous; ; LT = long-term; M = male; MCV = mean corpuscular volume;

PN = parenteral nutrition; RR = reference range; Se = Selenium; TE = trace elements; TPN = total parenteral nutrition; ULN = upper limits of normal; WBC = white blood cell

Source: Reviewer generated based on NDA 209379 Module 2.7.3

Table 5: Listing of Clinical Trials Relevant to NDA 209,379 (Pediatric Patients)

First Author, Year, Location	Study Objective	Patient Population, Number of Patients	Dose of Selenium IV and Duration	Reported Findings	Comments Relevant to the Proposed Indication
Daniels 1996 [6] Australia	To determine whether Se supplementation of parenteral nutrition with 3 mcg/kg/day is safe and effective in improving the Se status of preterm infants.	Preterm infants <2000 g at birth without major congenital abnormalities, liver, or renal disease; expected to have PN for >5 days: PN + Se: N=19 Mean GA: 29 weeks PN – Se: N=19 Mean GA: 28 weeks Term BF=23 Mean GA not provided Term FF=8 Mean GA not provided	PN + Se: 3 mcg/kg/day + TE (zinc, copper, and manganese) PN – Se: TE (zinc, copper, and manganese) The mean duration of PN: <ul style="list-style-type: none">• PN – Se: 19 days (range=6 to 28 days)• PN + Se: 18 days (range=6 to 33 days)	<ul style="list-style-type: none"> • Baseline plasma and erythrocyte Se levels were not significantly different between PN + Se and PN - Se groups. • Over the initial 3 weeks, mean plasma Se level declined in PN – Se group while it was maintained in the PN + Se group. • At week 3, mean plasma Se was significantly lower in PN – Se group while it was maintained close to baseline in the PN + Se group, however by week 6 there was no significant net change in either group. • Numerically, mean erythrocyte Se level decreased in all groups except in Term BF group but was only statistically significant in the PN – Se group. • Urinary Se excreted was significantly higher in the PN + Se group compared to the PN-Se group. 	<ul style="list-style-type: none"> • Se supplementation of 3 mcg/kg/day was able to maintain plasma and erythrocyte GSHPx levels in preterm neonates receiving ≥75% of their energy from parenteral nutrition. • The initial difference in plasma Se levels at week 3, but not seen at week 6, could be due to progression to enteral feeds since the mean duration of PN was 18 to 19 days.

First Author, Year, Location	Study Objective	Patient Population, Number of Patients	Dose of Selenium IV and Duration	Reported Findings	Comments Relevant to the Proposed Indication
Huston 1991 [5] U.S.	To study the effect of Se supplementation in VLBW infants <1000 g.	Preterm VLBW (<1000 g) infants without evidence of congenital metabolic or chronic white blood cell disease: • PN + Se =10 ○ Mean GA: 26.7 weeks • PN – Se =10 Mean GA: 26.5 weeks	PN + Se: 1.5 mcg/kg/day + TE (zinc, copper, and manganese) PN – Se: TE (zinc, copper, and manganese) PN was administered until full oral feeding volumes were attained (mean age 42 days in both groups)	• Serum Se declined in both groups to lower levels compared to baseline but were significantly higher in the Se group at the time enteral feedings were initiated. The levels were equally low in both groups when PN was discontinued.	• Se supplementation at 1.5 mcg/kg/day in VLBW neonates was unable to maintain serum Se levels.

Abbreviations: BF = breast fed; F = female; FF = formula fed; GA = gestational age; GI = gastrointestinal; GSHPx = glutathione peroxidase; Hgb = hemoglobin; HPN = home parenteral nutrition; IV = intravenous; ; LT = long-term; M = male; MCV = mean corpuscular volume; PN = parenteral nutrition; Se = Selenium; TE = trace elements; TPN = total parenteral nutrition; ULN = upper limits of normal; VLBW = very low birth weight; WBC = white blood cell

Source: Reviewer generated based on NDA 209379 Module 2.7.3

7.2. Review Strategy

No clinical trials were conducted by the Applicant in support of this submission. However, the Applicant commissioned the ^{(b) (4)} to conduct a systematic literature review (SLR) to provide data supporting efficacy and safety of parenteral selenium. The protocol-based SLR of parenteral use of selenium in adults and pediatric populations was designed and reported in conformance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance [61]. Additionally, a SLR on the oral and enteral use of TEs was performed to supplement the parenteral route evidence. In the format of the framework requested by the Division (Appendix 17.4), a tabular summary of the published literature was submitted to support the efficacy and safety of parenteral selenium in adult and pediatric populations for the proposed indication.

^{(b) (4)} identified 72 publications including 58 publications reporting on selenium exposure in adults and 14 publications in pediatric populations (Table 6). All 72 articles submitted by the Applicant were considered individually.

Table 6: Number of Literature References Submitted by Applicant to Support Efficacy and Safety of Parenteral Selenium in Adults and Pediatric Populations

Publication on Study Type	Adult Population	Pediatric Population
Controlled studies	28	5
Observational studies	12	5
Case summaries	18	4
Total	58	14

Source: Reviewer generated based on Applicant submission for NDA 209379

7.2.1. Adults

A total of 58 publications reporting on adult exposure to parenteral Se were identified by the Applicant to support efficacy and safety. Of those, 11 publications were not applicable to the review due to the following reasons:

- 1 publication [70], reported an autopsy study of tissue concentrations in patients who had received home PN (HPN) and was not included.
- 10 publications [75-84] reported on studies that did not evaluate parenteral Se supplementation or contain information on blood Se levels.

The remaining 47 publications that reported on adult patients with parenteral Se supplementation alone or in combination with other TEs were reviewed for efficacy and safety.

7.2.2. Neonatal and Pediatric Populations

A total of **14** publications reporting on neonatal and pediatric exposure to parenteral Se were identified by the Applicant for possible inclusion to support efficacy and safety. Of those, 4 publications were excluded from the review:

- 2 publications [85, 86] reported on studies that did not evaluate parenteral Se supplementation or contain information on blood Se levels.
- 1 publication [87] was a duplicate reference [88].
- 1 case summary [89] described a patient with chromium deficiency and is therefore not applicable to this application.

The remaining **10** publications that reported on pediatric patients with parenteral Se supplementation alone or in combination with other TEs were reviewed for efficacy and safety.

It is worth noting that commercial PN formulas contain negligible quantities of selenium [90] and that selenium is generally added as a supplement prior to PN administration. Therefore, patients reported to be on HPN or TPN in studies are assumed to receive no additional selenium supplementation unless otherwise specified.

7.2.3. Additional Literature Not Identified by the Applicant

Additionally, the Division of Epidemiology (DEPI) conducted an independent review of the SLR submitted by the Applicant and identified 51 publications on patients receiving parenteral selenium or assessed selenium status in patients on PN not captured by (b) (4). For complete details, please see the complete consult review filed in DARRTS by Drs. J. Weissfeld, P. Bright, and S.K. Sandhu on March 12, 2019.

The publications identified by DEPI were also reviewed to support the efficacy and safety of parenteral Se for the proposed indication and are outlined in Table 7 by study design.

Table 7: Number of Publications Identified by DEPI Review Not Included in the Submission

Study Design	Study Population		All
	Adult	Pediatric	
Randomized controlled trials	6	1	7
Controlled studies (nonrandomized, interventional and observational)	5	4	8
Descriptive studies	12	7	20
Case reports	12	4	16
Total	35	16	51

Source: Adapted from DEPI Review for NDA 209379 by Drs. J. Weissfeld, P. Bright, and S.K. Sandhu

8. Clinical Evaluation

8.1. Review of Efficacy

8.1.1. Assessment of Selenium Concentrations

Central to the application review is to determine whether the published literature supports that parenteral selenium in the form of Selenious Acid Injection at the proposed dose (i.e., 60 mcg/day), will provide a nutrient source of selenium for patients that cannot tolerate oral/enteral nutrition. Selenium is currently marketed as a dietary supplement and its RDI value is 55 mcg/day for adults. The Applicant did not conduct bioavailability/bioequivalence studies comparing the oral to the intravenous formulation. However, as part of assessing the efficacy of the proposed intravenous formulation, the bioavailability of oral selenium, obtained from various food sources, e.g., plant, animal, supplements, etc. (expected to be on average %) and the adult and pediatric RDIs for oral selenium, were taken into consideration. Additionally, the Applicant provided literature reports assessing Se levels achieved after intravenous administration of various doses of selenious acid or sodium selenite, including doses higher than the proposed dose of 60 mcg/day in adults and 2 to 4 mcg/kg in pediatric population weighing less than ^(b) ₍₄₎ kg.

Multiple assays for assessing Se status (Table 8) have been developed based on measurements of total selenoproteins in blood or individual selenoproteins (e.g., glutathione peroxidase (GSHPx) activity in various blood components including plasma, erythrocytes, and platelets. Se levels can be measured extracellularly (e.g., plasma Se) and intracellularly (e.g., erythrocyte and platelet GSHPx-1). Se levels can also be measured in hair and nails but are limited by sampling reliability and complexity of analysis. Selenium levels tend to be less useful in non-deficient individuals because their selenoenzymes have maximized but may be useful in those patients who are on long-term PN who may be at risk for selenium deficiency [91].

Table 8: Common Selenium Assays and Range of Concentrations in Health Subjects Reported in Literature [92]

Type of Selenium Assays	Range of Selenium Concentrations as Reported in Various Literature Sources	Comments
Selenium Levels		
Whole blood Se	<ul style="list-style-type: none"> 14.68 to 24.73 mcg/dL [93] 	<ul style="list-style-type: none"> Reflect intracellular and extracellular Se, therefore range is higher than plasma Se Reflect Se intake over 3 to 4 months Slower responses to changes in dietary intake thus not commonly reported in studies
Serum/Plasma Se	<ul style="list-style-type: none"> Range of lower bound: 4.6 to 10 mcg/dL Range of upper bound: 10 to 16.5 mcg/dL 	<ul style="list-style-type: none"> Readily available Responds rapidly (within days to 1 week) to changes in selenium intake thus often used for supplementation studies Reference range may vary depending on geographical location and age Lower values in acute inflammatory state
Hair/Urine/Nail Se	<ul style="list-style-type: none"> RR not well established 	<ul style="list-style-type: none"> Assay not readily available Complex analysis Potential contamination from external sources (e.g., shampoo) Lack of standardized analytical assay
GSHPx Levels		
Plasma GSHPx	<ul style="list-style-type: none"> RR not well established 	<ul style="list-style-type: none"> Readily available Correlates with plasma Se levels Only reflective of ~20% of total plasma Se
Erythrocyte (RBC) GSHPx	<ul style="list-style-type: none"> RR not well established 	<ul style="list-style-type: none"> Assay not readily available More reflective of selenium status over a longer time period relating to RBC lifespan
Platelet GSHPx	<ul style="list-style-type: none"> RR not well established 	<ul style="list-style-type: none"> Assay not readily available

Abbreviations: GSHPx = glutathione peroxidase; RBC = red blood cell; RR = reference range; Se = selenium

Source: Reviewer generated based on literature review

Assays to measure serum and plasma Se levels are the most widely available assays in clinical practice and are most often reported in the assessment of selenium deficiency. No significant differences have been found between plasma and serum Se levels [94]. However, the plasma compartment corresponds to only a small part (<2%) of the body selenium content and may not adequately reflect the selenium status of the tissue compartment. It has been proposed that based on ongoing inflammatory processes, selenium may be redistributed from plasma into

body tissues and preferentially incorporated into different selenoenzymes, and after resolution of inflammatory processes, Se may be transferred back into plasma. Plasma GSHPx activity represents one of the selenoproteins present in the plasma and was the basis for establishing the RDI. Erythrocyte or red blood cell (RBC) Se and GSHPx levels are thought to provide a functional index of long-term selenium status due to the longer lifespan of erythrocytes (i.e., approximately 3 months). As a result, RBC selenium levels may not show noticeable short-term changes in levels during treatment of deficiency or dietary supplementation [95-97].

Determining whether there is a correlation between results from the various Se assays and endogenous selenium stores can be challenging due to 1) lack of a well-established “normal” range; 2) multiple external factors that can affect assay results; and 3) inconsistent results between the various assays.

There are no uniformly accepted “normal” ranges for systemic Se concentrations in the body. Several studies have tried to assess Se levels in healthy subjects to establish a referenced standard; also, laboratory reference ranges have been developed using various assays. For example, plasma Se has a reported laboratory reference standard range between 2.3 and 19 mcg/dL, depending on the instrument manufacturer [97-99]. Based on published studies enrolling North American populations, the reported ranges have varied between 9.5 to 16.5 mcg/dL [45, 63, 100]. The Center for Disease Control measured serum Se concentrations in the U.S. population in National Health and Nutrition Examination Survey (NHANES) III conducted through 1988-1994 and found that the range of serum Se concentrations (5th and 95th percentile) was between 10.03 to 15.41 mcg/dL [101]. However, Jain and Choi [93] reported on data from NHANES for the period year 2011–2012 which showed blood Se concentrations at 5th and 95th percentile to be 15.34 and 23.62 mcg/dL, respectively. For ages ≥12 years, males were found to have 3% higher blood Se level compared to females. Selenium intake was above the RDI regardless of age, sex, race, or family and ranged between 80.9 to 201.5 mcg/day. While results from the NHANES for year 2011-2012 suggest that the range of Se concentrations in the U.S. population is increasing compared to results from 1988 to 1994, which is consistent with the finding of increased selenium intake in the diet; it cannot be considered conclusive because the authors did not specify whether blood Se concentrations referred to plasma/serum or whole blood Se concentrations. Finally, while a given selenium concentration range may be representative of the local population, levels outside this “normal” range may not necessarily reflect functional deficiency or toxicity.

Reference ranges for Se assays have not been well established in neonatal and pediatric populations. In neonates, evidence is conflicting whether any differences in the reference range exists between preterm and term neonates. Lockitch et al. (1989) [102] reported plasma Se and GSHPx activity levels obtained within 72 hours after birth in healthy term neonates in Canada to be numerically higher compared to preterm, low birth weight neonates (Appendix 15.8). Other studies have reported blood Se levels in preterm neonates to be between 6.5 to 10 mcg/dL [103], suggesting that they may require higher doses of selenium due to increased metabolic requirements. While the mean Se levels in these studies overlap, the wide range of reported Se levels further emphasizes the lack of a well-established normal reference range. There is also some evidence to suggest that serum Se levels may increase with age. A study of 1010 healthy

children (age range: 1 day to 18 years) demonstrated that serum Se levels were significantly higher in older children compared to those <1 year old, suggesting the need for age-appropriate reference values in pediatric populations [104].

Several factors may contribute to the variations observed in serum Se concentrations including age, sex, food intake, and geographical area (i.e., Se content in soil). Additionally, acute and chronic illnesses can also affect blood Se levels [95]. Plasma Se levels may be decreased in up to 40% of patients with trauma, post-surgical conditions, or systemic inflammatory response syndrome secondary to the underlying inflammatory response and presumably the resultant increased vascular permeability [105-107]. Therefore, some authors have proposed that the plasma Se levels be obtained with C-reactive protein (CRP) levels to allow interpretation of the results in the appropriate context due to CRP's role as an acute phase reactant [108, 109]. Plasma Se is also affected by other factors, including smoking, alcoholism, and some disease states such as chronic kidney disease [110] and HIV/AIDS [111].

Studies have not shown consistent correlation between Se levels and onset/development of clinical deficiency or toxicity. Similarly, there is also no clear correlation between severity of clinical symptoms and Se levels. Extremely low blood Se levels have been found in patients with no obvious clinical symptoms [112]. Therefore, the clinical significance of low Se levels has not been fully elucidated and should be interpreted in the overall clinical context.

Response time to changes in selenium intake can vary among different parameters used to measure selenium [4]. A study by Sando et al. (1992) [4] reported that all parameters, i.e., plasma Se and GSHPx, erythrocyte Se and GSHPx, platelet GSHPx show decreased levels from normal baseline when selenium supplementation was withdrawn in 6 patients receiving long-term home TPN (mean 74.7 months) and increased again when selenium supplementation resumed. The response in platelet GSHPx was most rapid (within 1 week) of withdrawal and reintroduction of selenium supplementation. Plasma Se and GSHPx levels showed a significant decrease after 3 weeks without selenium supplementation while erythrocyte Se indices showed no significant change during that time span.

Despite the limitations in the selenium assays as discussed previously, there is extensive literature supporting maintenance of increased plasma or serum selenium concentrations in patients who receive parenteral selenium supplementation, regardless of baseline selenium status. Therefore, for the purposes of this NDA, it can be concluded that plasma/serum selenium concentrations can be used to provide an assessment of selenium status achieved after intravenous selenium administration. However, given the broad range of selenium concentrations reported in studies, the normal reference range for the U.S. population is uncertain. The label will convey a range that encompass the general reported reference values across studies to indicate levels below which insufficient supplementation may occur. Additionally, practitioners should interpret individual results in the context of their laboratory's reference range and clinical condition when assessing selenium status in patients.

8.1.2. Evolution of Studies Evaluating Parenteral Selenium Supplementation

Selenium was not recognized as an essential trace element until 1984, when it was recommended as an additive to PN by the American Medical Association [17]. Literature in the 1980s to 1990s described case reports and observational studies of patients on long-term complete PN (TPN) or partial PN who presented with symptoms suggestive of selenium deficiency with baseline low plasma/serum Se levels that improved with selenium supplementation. However, it is important to note that not all patients with plasma Se levels below the reference range developed clinical symptoms. Also, selenium supplementation in PN and monitoring of selenium levels were not standard practice during that time and therefore such patients who were on long-term PN were likely to develop selenium deficiency as described in the literature. Since then, there has been increased awareness of the need to supplement patients, especially those on long-term PN who are at risk of developing selenium deficiency. Subsequent studies focused on dose exploration to correct underlying selenium deficiency using healthy controls as a reference. In recent years, clinical studies have focused on exploring the role of high-dose selenium as an anti-oxidant and its effects on improving clinical outcomes in patients who are critically ill as well as cancer therapy; results from such studies have been inconclusive.

8.1.3. Review of Literature of Intravenous Selenious Acid Relevant to NDA

A total of 47 publications submitted by the Applicant to support efficacy of intravenous selenious acid in adults were reviewed. Two publications by Lane et al. (1987) [3] and Sando et al. (1992) [4] were considered the most relevant to support use of parenteral selenium as a nutrient source in patients on PN based on the study objectives and enrollment population. These studies are discussed separately in more detail below. The remaining 45 publications are summarized in Section 8.1.3.3 and tabulated in Appendix 15.9 and 15.10.

8.1.3.1. Lane et al. (1987) (U.S.) [3]

Title:

The effect of selenium supplementation on selenium status of patients receiving chronic total parenteral nutrition.

Study Objective:

The purpose of this study was to determine the effect of parenteral selenium (as selenious acid) on the selenium status of patients on TPN.

Study Design:

A three-part non-randomized, controlled study that evaluated effect of parenteral Se on plasma and urinary Se concentration and platelet and erythrocyte GSHPx activity of U.S. patients on PN compared to healthy controls.

Study Population:

Investigators enrolled 7 patients (3 males and 4 females) with malabsorption who had been on TPN for more than 1 year. Mean age was 44 years and age ranged from 31 to 52 years. The patients did not receive enteral nutrition.

A healthy control group included 8 sex-, age-, and weight-matched subjects.

Study Treatment and Duration:

Patients on PN received supplemental selenium as follows:

- 1) No parenteral selenium x 1 month
- 2) 80 mcg/day of parenteral selenium x 1 month
- 3) 160 mcg/day of parenteral selenium x 1 month

Following evaluation of the selenium 160 mcg/day dose, all patients were returned to the prescribed supplementation dose of Se (80 mcg/day). Several months later, additional urine and blood collections, and a 3-day, 24-hr diet history were completed by 4 TPN patients to evaluate their response to lowering the parenteral selenium dosing from 160 to 80 mcg/day.

All controls consumed a normal diet containing approximately 50 to 200 mcg selenium/day. Calculation of dietary selenium was based on reported diet history and computer-based dietary analysis using a nutrient database.

Outcomes Assessed:

Investigators evaluated the effect of selenium supplementation on plasma, erythrocyte, platelet Se and GSHPx activities levels.

Summary of Reported Findings:

Plasma Se concentration, platelet and erythrocyte glutathione peroxidase activity, and urinary selenium increased with increasing levels of parenteral selenium (Table 9). During the time patients received 160 mcg/day selenium supplementation, patient plasma Se concentrations increased from 28% to 58% of the control levels. At selenium supplementation of 160 mcg/day, no statistically significant difference was observed between the patients and controls in Se levels or platelet glutathione peroxidase activity.

Several months (not specified by the investigators) after completing supplementation using the 160 mcg/day dose and switching to the 80 mcg/day dose, blood and urine were collected from four patients to evaluate their response to lowering the parenteral selenium dose from 160 to 80 mcg/day (Figure 3). Three patients had decreasing platelet glutathione peroxidase activity, while plasma selenium concentration decreased in two patients.

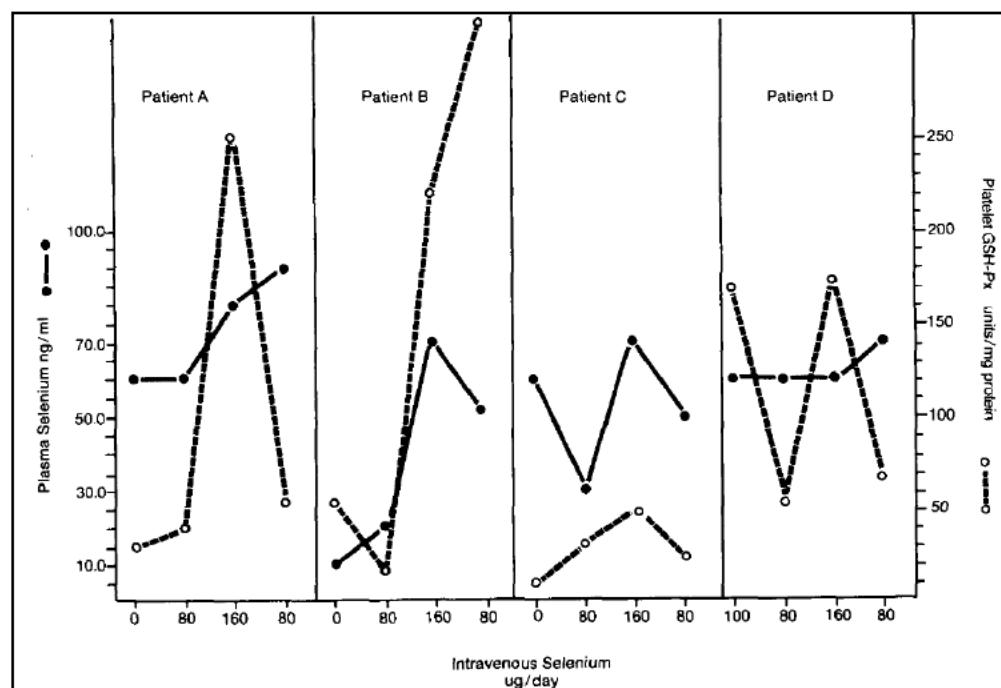
Table 9: Mean (Standard Error) Plasma and Urinary Selenium Concentration and Platelet and Erythrocyte Glutathione Peroxidase Activity in Total Parenteral Nutrition Patients and Control Subjects

Parameter	Level of Parenteral Selenium Supplementation (N=7)			Controls (N=8)
	0	80 mcg/day	160 mcg/day	
Plasma Se (mcg/dL)	3.40 (0.6)	5.0 (0.2)	7.0 (0.2)	12.0 (0.3)
Platelet GSHPx activity (U/mg protein)	45.9 (6.6)	97.0 (6.4)	160.0 (17.0)	194.0 (20.4)
Erythrocyte GSHPx (U/g hemoglobin)	7.8 (3.5)	16.5 (4.4)	Not performed	19.3 (1.7)
Urinary Se (mcg/day)	23.0 (3.8)	34.0 (1.9)	72.0 (1.1)	39.0 (2.9)

GSHPx = glutathione peroxidase; Se = selenium

Source: Lane et al. (1987)

Figure 3: Effect of Intravenous Selenium on Plasma Selenium Concentration and Platelet Glutathione Peroxidase Activity in Four Patients



Abbreviations: GSHPx = glutathione peroxidase

Note: The order of the selenium dosage (0, 80 mcg/day, 160 mcg/day, 80 mcg/day) is from left to right.

Source: Lane et al. (1987)

Conclusions:

This study evaluated patients on long-term chronic PN with no additional oral/enteral supplementation. Using Se levels from matched healthy controls as reference ranges, results from this small study demonstrated that intravenous selenious acid did provide a source of selenium in patients dependent on PN as illustrated by corresponding increases in plasma Se level and GSHPx enzyme activity. While this increase was greater when supplemented with 160 mcg/day compared to 80 mcg/day, Se levels in supplemented patients on both doses were still below the corresponding levels in healthy controls; however, the authors indicated that the 160

mcg/day dose achieved Se concentrations similar to healthy controls reported in a previous study (reference was not provided). The authors did not specify whether patients received selenium supplementation prior to study entry, therefore it is unclear whether they could have been selenium deficient at baseline and therefore may have a higher requirement compared to those that did not have underlying deficiency. Additionally, the authors did not report whether clinical symptoms of Se deficiency were assessed at baseline and throughout the study period. Thus, the clinical significance of the low plasma Se levels is unclear.

It is interesting to note that when the parenteral selenium dose was decreased from 160 to 80 mcg/day, changes in plasma Se and platelet GSHPx were variable (Figure 3). Two patients (patients A and D) showed a continued rise in plasma Se levels while a decline was observed in patients B and C. The variable responses seen in plasma Se after a decrease in the dose of Se supplement from 160 mcg to 80 mcg suggest that fluctuations in Se levels may exist from month-to-month. Also, since the investigators did not specify when the Se levels were obtained after the dose reduction and whether the levels were obtained at the same time for each patient, it is unclear whether these factors may have had an impact on the results. Three patients (patients A, C, and D) showed a decrease while patient B showed continued rise in platelet GSHPx activity suggesting that additional studies are needed to verify correlation between platelet GSHPx activity and Se status in patients on HPN.

Urinary selenium increased with increasing doses of selenium supplementation (dietary or parenteral) and as such was noted to be excreted at all selenium levels. The investigators reported total mean urinary selenium excretion increased to 23 at a dose of 0 mcg/day, 34 at 80 mcg/day, and 72 at 160 mcg/day compared to control patients who excreted 39 mcg/day suggesting that increased urinary excretion was correlated with increased parenteral selenium dosing. The small number of subjects in this study limits broader generalization of these results.

8.1.3.2. Sando et al. (1992) (Japan) [4]

Title:

Platelet Glutathione Peroxidase Activity in Long-Term Total Parenteral Nutrition with and without Selenium Supplementation

Study Objective:

The purpose of this study was to evaluate the effect of parenteral selenium on Se levels using various parameters in long-term TPN patients.

Study Design:

Non-randomized, controlled study.

Study Population:

Investigators enrolled 6 Japanese patients (5 females and 1 male) with a history of chronic gastrointestinal disease on long-term home TPN lacking selenium (37 to 156 months; mean 74.7 months). Age of the patients ranged from 4 to 38 years (mean=26 years) old. The control population consisted of 26 healthy adult volunteers, (20 males and 6 females), age 22 to 40 years old with a mean age of 29 years.

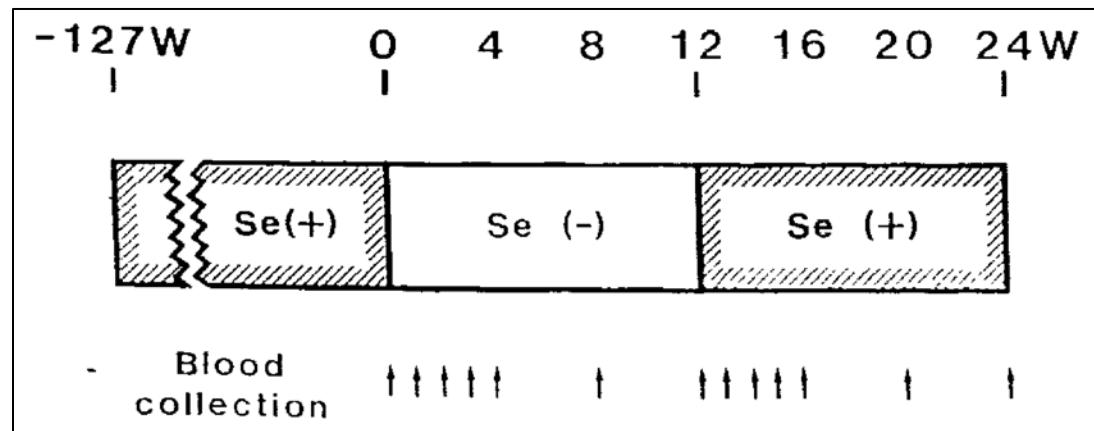
Outcomes Assessed:

Investigators evaluated the effect of selenium supplementation on plasma, erythrocyte, and platelet Se levels.

Study Treatments and Duration:

All patients received parenteral selenium supplementation (adults: 200 mcg/day and children: 7 to 10 mcg/kg/day) for 127 weeks. Se concentration and GSHPx activity in plasma, erythrocytes and platelets (GSHPx only) were measured monthly for the 127 weeks of TPN and were reported to be maintained within the pre-specified normal range. Selenium supplementation was then discontinued for 12 weeks, and then reinitiated for another 12 weeks. Blood samples for determining plasma and erythrocyte Se and GSHPx levels were collected according to the schedule shown in Figure 4.

Figure 4: Study Design



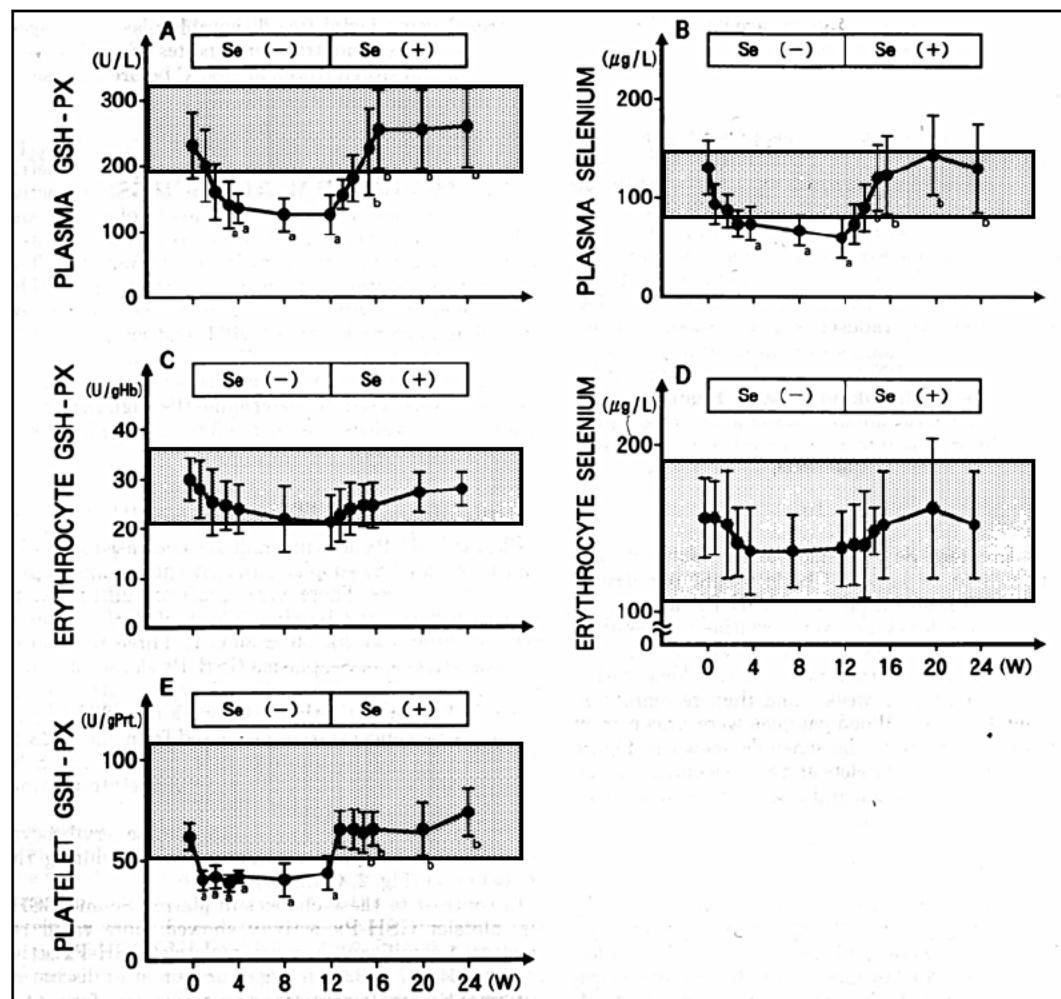
Abbreviations: Se = selenium; W = weeks
Source: Sando et al. (1992)

Summary of Reported Findings:

After discontinuation of selenium supplementation, the Se levels measured by all parameters decreased significantly within 3 weeks. Clinical symptoms of deficiency during the 12 weeks without supplementation were not assessed or reported by the investigators. When selenium supplementation in TPN was resumed, Se levels measured by all parameters started to increase, although the plasma Se level was the only value that increased significantly within the 3 weeks of re-initiation. Four weeks after re-initiation of selenium supplementation, all of the Se levels were within the range established using healthy controls. While plasma and platelet Se

levels in non-supplemented patients declined to outside the reference range, erythrocyte Se and GSHPx activities did not, despite showing a declining trend.

Figure 5: Changes in Se Indices (Mean and SD) During Discontinuation of Selenium Supplementation and Re-Initiation of Selenium Supplementation



Abbreviations: a = p<0.05 comparing mean to Week 0; b = p<0.05 comparing mean to Week 12; GSHPx = glutathione peroxidase; SD = standard deviation; Se = selenium

Note: Shadowed areas represent the healthy control ranges.

Source: Sando et al. (1992)

Conclusions:

In this small study, the investigators established that adult and pediatric patients on TPN who received IV selenium supplementation (200 mcg/day in adults and 7 to 10 mcg/kg/day in children) achieved normal Se levels that declined within 12 weeks in response to Se withdrawal and rose again to normal levels compared to healthy controls after 4 weeks of reinitiating intravenous Se. Of all assays used, plasma Se level was consistently reflective of these changes in Se supplementation. It is likely that these patients required 200 mcg/day to maintain normal Se levels given they had received long-term TPN that was not supplemented by Se. Biochemical and clinical selenium status were not reported by the investigators.

This study suggests that plasma Se levels appear to respond earlier to selenium supplementation compared to erythrocyte Se levels, likely relating to the longer lifespan of erythrocytes [96] which are more reflective of longer-term body stores. The small sample size in this study and the Japanese population limit generalizability of the results to a U.S. population.

8.1.3.3. Summary of Other Pertinent Studies Evaluating Parenteral Selenium in Adults

The remaining **45** publications that reported on patients with parenteral selenium supplementation alone or in combination with other TEs are summarized below based on the available study information.

17 publications reported **randomized controlled** trials (RCTs) of selenium alone or in combination with other trace elements summarized below.

- 1 study (**Rannem et al. 1995**) [112] evaluated the effect of selenium supplementation on skeletal and cardiac muscular function in 10 patients on long-term PN. Ten adult patients were randomized 1:1 to receive 200 mcg/day of iv selenium or placebo for 4 months. After 4 months, the placebo-treated patients were administered selenium supplementation (200 mcg/day) in an open-label study for an additional 4 months. At baseline, all patients in both studies had lower Se levels (Table 10) compared to healthy controls suggesting that low blood Se levels are prevalent in patients on long-term HPN who have not been supplemented by selenium predisposing them to clinical deficiency. Four of the 10 patients reported symptoms of muscle weakness suggestive of clinical selenium deficiency. After 1 month of selenium supplementation, plasma Se increased to within the reference range in all patients. A similar effect was observed for plasma GSHPx activity (level not reported) in 9 out of 10 patients. This effect suggests that parenteral selenium supplementation at 200 mcg/day restored plasma Se levels and GSHPx activities. While it is unknown whether these levels could have been achieved with lower doses of selenium, it is likely these patients needed higher dose of Se given they had not received supplementation with IV Se over a long period and were selenium deficient. Continued selenium supplementation kept the plasma Se and GSHPx levels within the normal reference range. By month 4, all Se assays (plasma and erythrocyte Se and GSHPx) were within the reference range. All four patients with muscle complaints reported improvement in their symptoms with selenium supplementation. The results for this study suggest that plasma Se and GSHPx may respond more readily to a change in selenium supplementation compared to erythrocyte levels. However, it is important to note that the sample size is small in this study and the enrolled population were patients with known selenium deficiency and not those requiring a dietary source of selenium.

Table 10: Median (Range) Selenium and Glutathione Peroxidase in Plasma and Erythrocytes Before and After Supplementation With Selenium or Placebo

Assay Parameter	Reference Range	Selenium Supplementation (N=10)		Placebo (N=5)	
		Before	After 4 Months	Before	After 4 Months
Plasma Se (mcg/dL)	5.9 – 14.7	1.66 (0 - 5.45)	9.88 (7.11 - 17.9)	1.98 (0.55 - 3.95)	1.74 (1.66 - 3.95)
Plasma GSHPx (U/L)	217 - 504	64 (22 - 186)	280 (140 - 497)	89 (78 - 205)	84 (39 - 186)
Erythrocyte Se (mcmol/g Hgb)	3.1 – 6.2	1.9 (0.7 - 2.6)	3.5 (2.1 - 5)	1.6 (0.8 - 1.8)	1.9 (0.7 - 2.6)
Erythrocyte GSHPx (U/g Hgb)	11.4 - 40.9	8.5 (0 - 15.7)	21.6 (17.6 - 31)	8.3 (2.7 - 11.9)	8.4 (5.3 - 9.2)

Abbreviations: GSHPx = glutathione peroxidase; Hgb = hemoglobin; Se = selenium

Source: Rannem et al. 1995

- The remaining 16 publications [57, 99, 113-126] reported on studies that evaluated the effect of high-dose selenium supplementation in critically ill patients [e.g., systemic inflammatory response syndrome, elevated Acute Physiology And Chronic Health Evaluation (APACHE) II score, post-operative] at doses much higher than would be necessary for the proposed indication. These studies in critically ill patients are of limited applicability to establish efficacy for the proposed indication due to several factors including:
 - Critically ill patients have baseline lower blood Se assay levels due to presumed redistribution and increased loss via high output conditions such as polyuria and/or drains. Therefore, Se assay levels may not necessarily reflect Se tissue stores and the clinical status of these patients may more likely resemble that of selenium deficiency.
 - Study endpoints assessed were primarily clinical benefit outcomes such as mortality or duration of ICU stay. While most studies also assessed the effect of selenium supplementation on plasma Se and/or GSHPx activity, interpretation of the results is challenging given multiple confounders secondary to the complex clinical scenario of the enrollment population.
 - Selenium doses studied were at 4 to 67X (up to 4000 mcg/day) the Applicant's proposed dose and were studied for much shorter durations than would be expected for long-term intravenous parenteral nutrition.
 - Many of the randomized, controlled studies (13 of 16 studies) enrolled less than 50 patients per arm and therefore, results may not be generalizable to a larger population.

8 publications reported on non-randomized, controlled studies that enrolled patients on PN with selenium alone or in combination with other trace elements and are summarized below:

- 1 study by Rannem et al. (1993) [127] evaluated the effect of selenium supplementation on Se levels in patients on long-term HPN. At baseline, all patients had lower Se levels

(plasma Se median=1.66; range: 0 to 4 mcg/dL compared to healthy controls (plasma Se median=8.8 mcg/dL; range: 5.9 to 14.7 mcg/dL) suggesting that low blood Se levels can occur in patients on long-term HPN that has not been supplemented with Se and may be a predisposing factor to clinical deficiency. None of the patients displayed symptoms of selenium deficiency. Selenium supplementation at 200 mcg/day resulted in an increase in Se levels measured using various parameters in patients on HPN to within the reference range based on healthy controls. While the aim of the study was to evaluate the effect of parenteral selenium to correct clinical deficiency, subsequent reduction of selenium supplementation to 100 mcg/day did not appear to significantly affect the selenium levels or GSHPx activities suggesting that the reduction to a parenteral selenium dose of 100 mcg/day was sufficient to maintain plasma Se levels in patients on long-term TPN. Additionally, these results suggest that plasma Se levels and GSHPx activity may respond more readily to a change in selenium supplementation compared to erythrocyte assay levels.

- 2 studies by Reimund et al. [128, 129] showed that despite receiving HPN with selenium supplementation, patients in France still had low Se levels compared to healthy controls.
 - In **Reimund et al. (2000)**, investigators evaluated factors (e.g., liver biochemistry) associated with increased plasma manganese (Mn) concentration in HPN patients (N=21). Plasma trace element levels including selenium were measured. Plasma Se level was decreased in HPN patients compared to healthy controls (5.26 ± 1.93 mg/dL versus 7.13 ± 1.56 mg/dL, $P < 0.05$).
 - In **Reimund et al. (1999)**, investigators described their experience in establishing an outpatient HPN program including indications for HPN and patients' nutritional status evaluated by clinical (e.g., complications of HPN including catheter infections, venous thrombosis etc.) and laboratory parameters (e.g., electrolytes, trace element assays including Se etc.). Patients received HPN with "standard vitamin and trace element preparations (Nonan®; Aguettant, Lyon, France)", however, the exact amount of parenteral selenium supplementation was not specified. Plasma Se was decreased in HPN patients compared to healthy controls (5.51 ± 1.76 mg/dL versus 7.11 ± 1.53 mg/dL, $P < 0.05$) in this study also.

While, these combined study results suggest that patients on HPN have lower Se levels compared to healthy controls and may be at risk for clinical deficiency, neither study reported baseline Se levels, and the dose received in HPN was not standardized or reported. Therefore, the relationship between selenium supplementation and Se levels cannot be completely determined from these 2 studies.

- 2 publications by Baptista et al. (1984a, 1984b) [130, 131] described 2 studies based in the U.S. that assessed selenium status in patients on standard HPN (without selenium supplementation).
 - In **Baptista et al. (1984a)** [130], investigators assessed baseline selenium status by mean plasma concentrations and erythrocyte GSHPx activity expressed as

mcmol of NADPH oxidized/g Hb/min in 13 short bowel patients on HPN for a mean of 36 months (range 0.5 to 103 months) without administration of selenium supplementation. The mean plasma Se concentration in patients [4.51 mcg/dL (range 1.64 to 10.15 mcg/dL)] was significantly lower ($p<0.01$) than healthy controls [12.00 mcg/dL (range 9.94 to 14.35 mcg/dL)]. Similarly, mean erythrocyte GSHPx was also significantly lower compared to healthy controls [11.01 mcmol NADPH oxidized/gHb/min (range 0 to 28.47) versus 31.76 mcmol NADPH oxidized/gHb/min (range 13.06 to 51.62); $p<0.01$]. Additionally, four patients (plasma Se level between 1.64 to 4.31 mcg/dL) exhibited myalgia suggestive of clinical selenium deficiency, however there were no significant correlations between Se levels and the occurrence of symptoms, possibly due to the small sample size. The investigators concluded that patients with small bowel resections exhibited suboptimal selenium status and may be at risk of developing clinically evident selenium deficiency.

- In **Baptista et al. (1984b)** [131], investigators assessed the ability of selenious acid to reverse documented selenium deficiency in eight long-term home TPN patients as measured by restoration of plasma Se levels and erythrocyte GSHPx activity. Deficiency in patients was documented by comparing mean plasma selenium levels (3.59 mcg/dL) and erythrocyte glutathione peroxidase activity (8.93 mcmol NADPH oxidized/g Hgb/min) to those of 10 healthy controls (12.00 mcg/dL and 31.76 mcmol NADPH oxidized/g Hgb/min, respectively) ($p<0.002$). All patients received selenium 100 mcg/day added to the TPN solutions. At a later time (mean of 79 days), a blood sample was drawn from each patient to compare selenium assay levels with pretreatment levels and to levels of healthy controls. Mean plasma Se levels post-supplementation (10.35 mcg/dL) was significantly higher than pretreatment levels ($p<0.001$) and comparable to healthy controls. While mean erythrocyte glutathione peroxidase activity doubled following supplementation (17.56 mcmol NADPH oxidized/g Hgb/min), it was not significantly different from pretreatment levels. Result from this study suggested that the addition of 100 mcg/day selenium could restore suboptimal plasma Se levels in patients on home TPN but not GSHPx activity. Because the duration of parenteral supplementation varied greatly in this study (31 to 117 days; mean 79 days), it is difficult to conclude whether this may have impacted the Se level results. Thus, the lack of response in erythrocyte GSHPx activity level to parenteral Se supplementation may be due to either the small sample size, insufficient dosing or supplementation period.
- 1 study by **Lemoyne et al. (1988)** [132] evaluated the relationship between breath pentane (hydrocarbon gas evolved from the peroxidation of linoleic acid) and plasma levels of alpha-tocopherol (vitamin E), selenium, and Se-dependent GSHPx in nine patients on HPN (in Canada) with daily selenium supplementation of 119 mcg/day for 1 to 180 months duration (average 53 months). Results of this study showed that the mean plasma Se (11.06 mcg/dL in patients versus 13.43 mcg/dL in healthy controls) was lower in patients compared to healthy controls. However, applying a reference range of

10 to 14.4 mcg/dL for a Canadian population (Alfieri et al. 1998), the mean plasma Se for patients on HPN was still within the normal range suggesting that parenteral selenium supplementation of 119 mcg/day was sufficient to prevent biochemical deficiency. This conclusion is consistent with the finding of higher mean plasma GSHPx in patients versus controls (7 U in patients versus 5 U in healthy controls).

- 2 studies evaluated the effect of parenteral selenium supplementation in post-operative patients. Immediate post-surgical patients often have large fluid shifts and have other confounders that may affect the reliability of Se assays.
 - **Shenkin et al. (1987)** [133] compared trace element assay levels in 10 postoperative patients requiring PN for ≥7 days who were receiving complete premixed nutritive solution in a single bag versus 12 matched patients that received separate infusions (range of PN duration was 7 to 28 days and 8 to 28 days respectively) in the U.K. Both arms received Se 32 mcg/day and no significant difference was seen in serum Se levels between the two arms at all 5 time points of serum Se measurement (baseline, 1 to 5 days, 7 to 11 days, 14 to 18 days, and 21 to 25 days). Mean serum Se at all 5 measurements were within the reference range (6.32 to 15.8 mcg/dL) based on 100 patients admitted for elective orthopedic surgery and 50 laboratory healthy volunteers. Results from this study suggest that 32 mcg/day may be sufficient to maintain serum Se level within normal range in post-op patients on PN. However, it is important to note several limitations in this study in addition to the small sample size. The patient population was not previously PN dependent and thus at baseline was expected to have normal Se levels. Depletion of body store of selenium may require longer duration than the study duration and thus normal Se levels may not be reflective of overall body stores. Finally, the reference range used is lower than the reference range for U.S. population and results from this study may not be applicable to a U.S. population.
 - **Winnefeld et al. (1995)** [134] evaluated the effect of selenium supplementation in five post-gastrectomy patients that received a total of 584 mcg to 4100 mcg (58.4 to 410 mcg/day) parenteral selenium over 10 days post-operatively compared to four post-gastrectomy patients without supplementation. Investigators found that patients with selenium supplementation normalized whole blood and serum Se levels within 6 to 7 days while patients that did not receive supplementation showed levels below the reference range. However, results from this study are of limited applicability to the efficacy assessment based on the small sample size, variability in dosing, short duration of dosing and the enrollment population of surgical patients who may be predisposed to increased Se losses (such as from drains or ostomies) and deficiency or receiving doses targeted beyond the proposed indication.

8 publications (summarized in Appendix 15.9) reported on **observational studies** (Applicant referred to these as “uncontrolled” studies) of patients on HPN or TPN with selenium alone or in combination with other trace elements.

- In these studies, patients received parenteral selenium supplementation ranging from 40 to 400 mcg/day.
- Results of these studies are limited by the small sample sizes (N=5 to 57) and other confounders including lack of control for enteral selenium source and variabilities in the amount of selenium individual patients received within the same study.
- Despite these limitations, studies report a broad proportion (16 to 75%) of patients receiving selenium supplementation at doses of 40 to 69 mcg/day had levels below the normal reference range [45, 63, 69, 135], suggesting that a proportion of patients on PN may need selenium supplement beyond 60 mcg/day to achieve normal plasma Se level. However, the severity of underlying illnesses necessitating PN, doses administered, and selenium concentrations prior to enrollment in these studies were not always reported. In addition, the clinical significance of these findings is unclear as evidence of clinical deficiency was not reported.
- Selenium supplementation at or above doses of 100 mcg/day appeared to increase serum Se levels to within the reference range.

12 publications reported 15 **case summaries** on 15 patients presenting with symptoms suggestive of selenium deficiency (summarized in Appendix 15.10).

- Most patients were on PN with a duration ranging from 40 days to 7 years and reported serum/plasma Se levels below detectable levels or well below the reported reference range. In 2 case reports, patients were on PN for 5 and 19 days but both patients had an underlying Crohn’s disease and likely had low plasma Se prior to starting PN.
- Because of the few cases, variability in the Se assays used to determine selenium status, and lack of normal ranges provided to correlate with severity of selenium deficiency, it is difficult to ascertain a cut-off value below which symptoms of selenium deficiency develop or draw conclusions that correlate Se levels to development of specific symptoms from these case summaries. Serum Se levels in these case summaries were all below 5 mcg/dL.
- Reported signs and symptoms included cardiomyopathy (n=3), muscle weakness (n=5), myalgia (n=1), hair and nail changes (n=4), and neurological disturbances such as vision and speech impairment (n=1), gait disturbances (n=1), peripheral neuropathy with bilateral foot-drop (n=1), and encephalopathy (n=1).
- Patients who developed hair and nail changes, myopathy, and cardiomyopathy all reported improvement with parenteral selenium supplementation. Most patients received a dose between 80 to 250 mcg/day. One patient received 400 mcg/day of parenteral selenium.

- In contrast, no improvements were reported in the neurological symptoms despite selenium supplementation suggesting irreversibility when deficiency has progressed to this stage.

35 additional publications identified by DEPI review relating to parenteral selenium or selenium status in adult patients on PN are discussed below:

- 6 RCTs:
 - 5 publications (Berger et al. (2006) [136], Heyland et al. (2013) [137], Bloos et al. (2016) [138], Freitas et al. (2017) [139], and Schmidt et al. (2018) [140]) reported on studies that evaluated critically ill patients including ICU, post cardiac surgery, or burn patients at doses between 315 mcg/day to 4,000 mcg/day and therefore are of limited relevance to the proposed indication.
 - 1 publication (Forceville (2007) [141] summarized results from a trial reported in greater detail in a publication [115] already included by the Applicant in the submission.
- 5 controlled studies (nonrandomized interventional and observational):
 - 3 publications (Hayland et al. (2007) [100], Sakr et al. (2014) [142], Rehou et al. (2018) [143] reported on studies that evaluated critically ill patients including ICU, post cardiac surgery, or burn patients at doses between 315 mcg/day to 1,000 mcg/day and therefore are of limited relevance to the proposed indication.
 - Hatanaka et al. (2000) [144] investigated changes in serum and red cell Se levels and glutathione GSHPx activity in addition to urinary excretion of Se in 55 adult (>1 years old; N=49) and pediatric (\leq 15 years old; N=6) Japanese patients receiving long-term PN with and without Se supplementation. (see Appendix 15.9).
 - Frustaci et al. (2012) [144] evaluated the effect of Se 300 mcg on patients with malabsorptive conditions and idiopathic dilated cardiomyopathy in the setting of selenium and zinc (Zn) deficiency. Serum Se, myocardial Se content, and ejection fraction increased significantly in the Se supplemented group (n=10) compared to the untreated group (n=10). The authors emphasized the importance of monitoring trace element levels to prevent deficiencies. However, results of this study is of limited applicability to the proposed indication due to small sample size, coexisting zinc deficiency, much higher dosing, and patient population studied.
- 12 descriptive studies:
 - 8 studies (Mansell et al. (1989) [145]; Forceville et al. (1998) [107]; Dastych et al. (2016a) [146]; Salota et al. (2016) [108]; Theilla et al. (2017) [147]; Freitas et al. (2017) [148]; Van Gossum et al. (2017) [149]; Jafari et al. (2018) [150]) were determined to be not relevant to the efficacy analysis due to lack of selenium supplementation, selenium levels not assessed, significant deviation in study objective, enrollment population or dosing from the proposed indication.

- van Rij et al. (1979) [151] reported on the selenium status of 22 post-operative New Zealand patients receiving TPN for 10 or more days compared 12 surgical patients that did not receive TPN. Investigators found that even at baseline patients had significant lower plasma Se levels compared to controls (3.1 ± 0.4 mcg/dL versus 4.3 ± 0.4 mcg/dL) and the plasma selenium levels progressively declined with longer duration of TPN (10-20 days on TPN= 2.2 ± 0.2 mcg/dL versus >20 days on TPN= 1.5 ± 0.4 mcg/dL). The intake of selenium from TPN was less than 0.6 to 0.8 mcg/day. One patient with baseline low plasma Se (2.5 mcg/dL) developed symptoms of myalgia and muscle tenderness when plasma Se fell to 1.2 mcg/dL after 18 days of TPN. Her symptoms resolved after receiving 100 mcg/day of selenomethionine parenterally with TPN for 1 week and plasma Se increased to 2.2 mcg/dL. Continued supplementation of selenomethionine 100 mcg/day did not change plasma Se but the patient remained asymptomatic. Results from this study suggest that longer TPN duration is associated with lower plasma Se. Thus, patients on chronic TPN may need additional monitoring for early detection of selenium deficiency. Despite low plasma selenium, only 1 subject developed symptoms of selenium deficiency which resolved with 100 mcg/day of selenomethionine. Results of this study are limited by the patient population, small sample size and geographic location.
- Reimund et al. (2000) [152] analyzed TE status of 22 French HPN patients supplemented with 43.22 ± 16 mcg/day in females and 66.35 ± 33.5 mcg/day in males and compare them to clinical outcomes. Investigators found that patients on PN showed significantly lower levels of mean plasma selenium compared to healthy controls (5.72 ± 2.02 versus 7.49 ± 1.58 mcg/dL) but still within the normal range (5 to 10 mcg/dL) (see Appendix 15.9).
- Dastych et al. (2016b) [153] evaluated TE levels in 68 patients in the Czech Republic with short bowel syndrome on long-term TPN (mean duration 33.5 months; range 4 to 96 months). Patients received a mean parenteral selenium supplementation of 24 mcg/day (range 17 to 32 mcg/day). Reference range for whole blood Se was established using healthy adults and found to be 8.5 (7.11 to 9) mcg/dL. Median whole blood Se (6.08 mcg/dL; interquartile range (IQR) 5.21 to 7.58 mcg/dL) was found to be significantly lower than healthy controls ($P > 0.005$). Forty percent of patients had a Se level below the reference range although no clinical signs of selenium deficiency were observed in these patients. Patients in this study had several risk factors of selenium deficiency including long-term TPN, underline intestinal failure, and received a lower dose of selenium supplementation than the proposed dose. Therefore, the high proportion of patients with Se blood levels below the reference range is consistent with prior studies.
- Uzzan et al. (2017) [135] evaluated the prevalence of low TE in 73 French patients with chronic intestinal failure (defined as need of parenteral support (energy and/or intravenous fluid requirement) at least 8 times a month) and on

PN with TE supplement for at least 3 months. All patients received sodium selenite 70 mcg/day. Mean PN duration was 8.9 years. Mean PN infusion frequency was 4.8±1.8 days per week. Mean serum Se was 8.93±2.37 mcg/dL. Sixteen (21.9%) of patients had serum Se levels below the reference range (7.11 to 11.85 mcg/dL). Investigators reported no overt clinical manifestations of TE deficiency were noted. Results from this study suggested that a proportion of patients on selenium supplementation of 70 mcg/day still had Se levels below the referenced range.

- 12 case summaries:
 - 7 cases [42, 154-159] that described patients with signs and symptoms attributed to selenium deficiency including acrodermatitis, cardiomyopathy, and congestive heart failure.
 - 5 cases reports [160-164] of patients with signs and symptoms attributed to other TE deficiencies or high manganese level.

8.1.4. Review of Relevant Literature of Intravenous Selenious Acid in Neonatal and Pediatric Populations

A total of 10 publications submitted by the Applicant to support efficacy of intravenous selenious acid in pediatric patients were reviewed. Two publications by Huston et al. (1991) [5] and Daniels et al. (1996) [6] reporting on controlled studies in neonates receiving PN were considered to be the most relevant to the proposed indication based on study design and enrollment population. These studies are further discussed below.

8.1.4.1. Huston et al. (1991) [5]

Title:

Selenium Supplementation in Low-Birthweight Premature Infants: Relationship to Trace Metals and Antioxidant Enzymes

Study Objective:

The purpose of this study was to assess the effect of selenium supplementation in very low birth weight (VLBW) infants less than 1000 grams (g).

Study Design:

Prospective, randomized, controlled study.

Study Population:

Twenty American preterm low birthweight (less than 1000 g) infants without evidence of congenital metabolic or chronic white blood cell disease were enrolled. The mean gestational age (GA) was 26.7 and 26.5 weeks in the selenium supplementation and no selenium supplementation PN groups, respectively.

Study Treatment and Duration:

Patients were randomized into PN with selenium supplementation (PN + Se) at 1.5 mcg/kg/day and PN without selenium (PN – Se). All patients received other trace elements including zinc, copper, and manganese. PN was administered until full oral feeding volumes of 150 ml/kg/day were attained. Data on duration of PN was not reported. Blood samples were collected before initiation of TPN (Sample A), at time of oral feed initiation (Sample B), and at time of full oral feed (Sample C).

Summary of Reported Findings:

Serum Se concentration was reported in 8 of the 10 patients in each arm and declined in both groups to lower than baseline. Se levels were significantly higher in the group of neonates with selenium supplementation at the time enteral feedings were initiated (Table 11) compared to neonates that did not receive selenium supplementation (Sample B). However, the Se levels were equally low when PN was completely discontinued at time of full oral feed (Sample C).

Table 11: Change in Serum Selenium Over Time

Group	Serum Selenium (Mean \pm SD in mcg/dL)		
	Before TPN (Sample A)	Initiation of Oral Feed (Sample B)	Full Oral Feed (Sample C)
PN – Se (N=8)	6.2 \pm 8	3.7 \pm 5	3.6 \pm 14
PN + Se (N=8)	7 \pm 15	5 \pm 6	3.8 \pm 18

Abbreviations: PN = parenteral nutrition; SD = standard deviation; Se = selenium; TPN = total parenteral nutrition

Source: Adapted from Huston et al. 1991

Conclusions:

While the small sample size limits interpretation and generalization, these results suggest that 1.5 mcg/kg/day of Se supplementation was unable to maintain serum Se at baseline levels in preterm low birthweight neonates which is consistent with the knowledge that preterm neonates have higher metabolic/energy requirements (). While the serum Se levels were numerically higher at time of initiation of enteral feeds, the lack of difference in Se levels between the 2 arms at time of PN discontinuation (i.e., Sample C, full oral feeds) is likely due to removal of the intravenous selenium nutrient source; however, the duration of PN in each arm was not reported. Many other factors including the overall health status and duration of PN with selenium supplementation were not reported for each cohort and may have confounded interpretation of these results.

8.1.4.2. Daniels et al. (1996) [6]

Title:

Randomized clinical trial of parenteral selenium supplementation in preterm infants.

Study Objective:

The purpose of this study was to determine whether selenium supplementation of parenteral nutrition with 3 mcg/kg/day is safe and effective in improving the selenium status of preterm infants.

Study Design:

Prospective, randomized, Investigator-blind, controlled, parallel-group study.

Study Population:

Australian preterm infants less than 2000 g at birth (n=38) without major congenital abnormalities, liver, or renal disease and expected to have PN for >5 days. The mean gestational age and birth weights were similar between the two arms (PN + Se: 29 weeks and 1129 g, respectively; PN - Se: 28.0 weeks and 1211 g, respectively). The age at which enteral feeding was started and completely established were also similar for both groups (PN + Se =19 days and PN - Se =18 days).

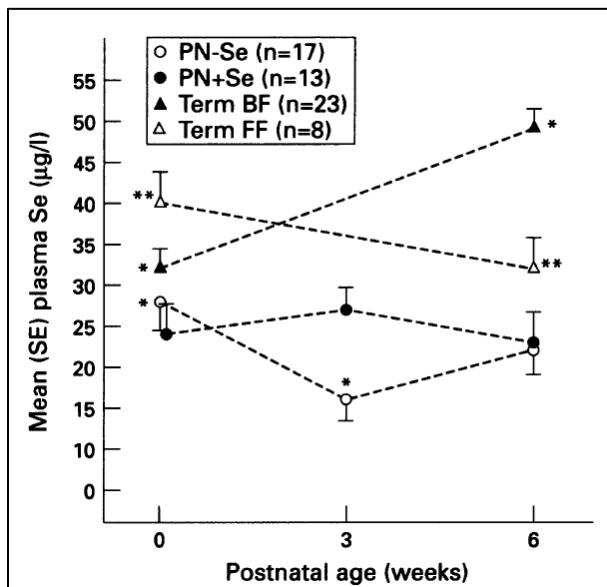
Study Treatment and Duration:

Patients were randomized to receive PN + Se (3 mcg/kg/day) (n=19) or non-supplemented PN - Se (n=19) initiated within 72 hours of life and reduced as enteral feeds were introduced. The study also included a reference group of healthy term infants (23 breastfed and 8 formula-fed). The mean duration of PN was 19 days (range=6 to 28 days) in the PN - Se cohort and 18 days (range=6 to 33 days) in the PN + Se cohort.

Summary of Reported Findings:

Initially, there was no difference in plasma or erythrocyte Se or GSHPx activities between the preterm neonate arms. Over the first 3 weeks of life, plasma Se declined in the non-supplemented group by 1.33 mcg/dL (p=0.001, n=17), but was maintained in the supplemented group (Figure 6). At Week 3, plasma Se was significantly lower (p=0.026) in the non-supplemented (PN - Se) group. Numerically, mean erythrocyte Se levels decreased in all groups except in term breast fed group but was only statistically significant in the PN - Se group. The amount of urinary Se excreted was significantly higher in the PN + Se group compared to the PN - Se group.

Figure 6: Changes in Mean Plasma Se Over the First Six Weeks of Life in Non-Supplemented (PN – Se) and Supplemented (PN + Se) Preterm Infants Compared With Term Breast Fed and Formula Fed Infants [6]



Abbreviations: BF = breast fed; FF = formula fed; PN = parenteral nutrition; SE = standard error; Se = selenium

Source: Daniels et al. (1996)

Conclusions:

Parenteral selenium supplementation at 3 mcg/kg/day was demonstrated to be sufficient to maintain mean plasma levels in preterm neonates on PN. The subsequent increase in mean plasma Se in the PN – Se group between week 3 to 6 could be due to switch to enteral feeding since the mean onset of enteral feeding initiation was at 18 to 19 days. Higher levels of Se excretion is difficult to interpret because there was no correlation between changes in plasma Se and urinary excretion.

8.1.4.3. Summary of Other Pertinent Studies Evaluating Intravenous Selenious Acid in Neonatal and Pediatric Populations

The 8 publications that reported on pediatric patients with parenteral selenium supplementation alone or in combination with other TEs are summarized below based on the available study information:

- **1 publication by Darlow et al. (2000)** [165] reported on a RCT evaluating the effect on clinical outcomes of selenium supplementation in very-low-birth-weight infants (less than 1500 g) achieving levels comparable to term breastfed neonates. In this study based in New Zealand, 534 neonates were randomized 1 :1 to receive intravenous or oral selenium (n=268) (7 mcg/kg/day when fed parenterally or 5 mcg/kg/day when fed enterally) or placebo (n=261) (no parenteral supplement and 0.5 mL/kg/day of sterile water when fed enterally) initiated at Week 1 of life until postmenstrual age (gestational age plus chronological age) of 36 weeks or discharge home, if earlier. Investigators evaluated the effect of selenium supplementation on clinical outcomes including oxygen

dependency at 28 days of age and total number of days of oxygen dependency. Secondary outcome measures included death, retinopathy of prematurity, nosocomial sepsis beyond 1 week of age, and days to discharge home, etc. Mean plasma Se and glutathione peroxidase concentrations were obtained in mothers and in infants prior to randomization and at 28 days and at 36 weeks' postmenstrual age. There were no differences between arms in the pre-randomization plasma Se and GSHPx concentrations. Mean plasma Se concentrations were 2.6 mcg/dL before randomization in both arms and at 28 days had risen in the selenium supplemented group to 4.4 mcg/dL but fallen in the control group to 2.3 mcg/dL ($p<0.0001$) without supplementation. Selenium supplementation had a lesser effect on plasma GSHPx activity than on Se concentration but plasma GSHPx still increased by 5.4 U/L in the selenium supplemented arm in contrast to a decrease of 14.2 U/L in the placebo arm ($p<0.001$). There was no association between clinical outcome measures and Se concentrations at 28 days or 36 weeks' postmenstrual age. While parenteral selenium supplementation of 7 mcg/kg/day did not improve neonatal outcomes in this trial, it provided evidence of an increase in plasma Se and GSHPx levels compared to a decrease in these levels in low birth weight neonates that did not receive supplementation. Of note, the selenium dose studied was 2 to 3 times higher than the standard U.S. practice guideline recommendation of 2 mcg/kg/day (i.e., A.S.P.E.N.). Given that populations residing in geographical regions (including New Zealand) with low selenium soil content may have underlying low selenium body stores in addition to the investigators' assessing clinical outcomes, a higher dose may have been studied for these reasons and may be appropriate to maintain selenium levels in such populations.

- **4 publications** reported on an **uncontrolled** study of selenium alone or in combination with other trace elements in pediatric patients on chronic PN (summarized in Appendix 15.11). All 4 publications described clinical selenium deficiency in patients requiring long-term PN. Selenium supplementation ranged from 2 to 5 mcg/kg/day. Precise dosing could not be determined in the Davis et al. (2014) [166] publication because weights were not reported in patients.
- **3 publications** reported case studies of pediatric patients presenting with symptoms of selenium deficiency (summarized in Section 15.12).

16 additional publications identified by DEPI review relating to parenteral selenium or selenium status in pediatric patients on PN are discussed below:

- 1 RCT: Winterbourn et al. (2000) [167] summarized results from a trial more fully reported in a Darlow et al. (2000) [165] already included by the Applicant in the submission and discussed above.
- 4 controlled studies (nonrandomized interventional and observational):
 - Aschner et al. (2015) [168] did not assess selenium status and therefore is not relevant to this application.

- Chen et al. (2016) [169] reported on a retrospective study conducted in the U.S. that evaluated the effects of selenium shortage on mean selenium dosing (between 0 and 9 mcg/kg/day) in 37 PN dependent infants less than or equal to 1 year. Investigators found that while the mean selenium dose decreased 2-fold during the shortage (2.1 ± 1.2 mcg/kg/day; range: 0.2–4.6 mcg/kg/day) versus the non-shortage period (3.8 ± 1 mcg/kg/day; range: 2.4–6 mcg/kg/day; $P<0.001$). There was no significant difference in the number of patients with serum selenium levels below the normal range. Given the study designs, broad range of doses, and the small number of subjects, interpretability of the study results is limited.
- Johnsen et al. (2017) [97] reported on a retrospective study conducted in the U.S. comparing hospitalized pediatric patients and receiving PN (without enteral nutrition) that contained selenium (3 mcg/kg/day) and manganese (1 mcg/kg/day) to those that received PN without. Serum Se levels were measured at a mean of 20 days for supplemented patients (n=131) and 19 days for non-supplemented patients (n=57) with no difference between groups ($P=0.2973$). Additionally, the majority of the patients (78% and 93%, supplemented and non-supplemented respectively) had serum Se levels within the normal referenced range (2.3–19 mcg/dL). It is unclear why the non-supplemented patients had a higher proportion of patients with serum Se levels within the normal range. Information on potential confounders such as baseline Se level, underlying clinical condition, and duration of PN prior to enrollment were not reported which may contribute to the result. Despite these limitations, results from this study suggest that most hospitalized pediatric patients are not deficient and have normal serum Se levels after 3 weeks of no selenium supplementation.
- Freitas et al. (2018) [170] analyzed the selenium status of four critically ill Brazilian hospitalized pediatric patients (ages 11 to 14 years old) on PN for 14 days supplemented with 2 mcg/kg/day of selenious acid to 10 admitted critically ill control patients (ages 4 months to 15 years old). Patients were found to have low Se levels at all measured time points regardless of Se supplementation. Given the small sample size, critically ill enrolment population, and geographical location, results of this study are of limited applicability to the proposed indication in a U.S. population.

- 7 descriptive studies:
 - Klinger et al. (1999) evaluated whether selenium supplementation at 2 mcg/kg/day maintained plasma Se levels and the relationship between selenium supplementation and hypothyroidism in ELBW preterm Israeli neonates. The investigators found that plasma Se remained low despite supplementation of 2 mcg/kg/day. Baseline and subsequent Se levels were not reported. Therefore, it is difficult to draw conclusions about the effect of parenteral selenium supplementation in pre-term neonates based on this study (see Appendix 15.11).

- 4 publications (Yang et al. (2011) [171]; Namjoshi et al. (2017) [35]; Smith et al. (2018) [172]; Neelis et al. (2018) [173]) did not include selenium dosing of individual patients and selenium levels and therefore could not contribute to the efficacy analysis. However, investigators from these studies reported that serum selenium below the reference range in patients on PN ranged between 16 to 35%. The authors did not report on assessment of clinical signs and symptoms of selenium deficiency.
- Greene et al. (2016) [174] did not assess selenium status and therefore is not relevant to this application.
- Dressler et al. (2018) [175] evaluated the efficacy and safety of ketogenic PN, which included selenium 8 mcg/day (4 ml of Peditrace® containing 2 mcg/ml), in 17 Austrian children with epileptic encephalopathies. This publication was determined not relevant to the review of efficacy due to the dose, study population and study objective.

- 4 case summaries:
 - 3 cases summaries (Lockitch et al. (1990) [176-178]; Hirato et al. (2003) [177]; and Yun et al. (2017) [178]) described patients with signs and symptoms of selenium deficiency including nail changes, cardiomyopathy and neurological deficits including gait disturbances and muscle weakness.
 - 1 case summary (Moser et al. (2016) [179]) of a patient with pancytopenia that was attributed to copper deficiency and therefore not relevant to this application.

8.1.5. Specific Populations

Literature evidence for selenium requirements in pregnancy, while scant, suggests that pregnant women have an increased metabolic demand for trace elements, including selenium due to fetal needs. Selenium deficiency has been reported to be associated with adverse pregnancy (e.g., miscarriages) and fetal outcomes (e.g., low birth weight). Because selenium is secreted in breast milk, it would be reasonable to assume that lactating women may also need higher doses of selenium for their average daily requirements.

Burn patients are noted to have increased energy expenditure and subsequent increased nutritional requirements based on the literature. Berger et al. [149] attempted to determine the selenium losses and balances in 10 patients with burns greater than 32±9% total body surface area and found that cutaneous loss of selenium on operative days contributed to an overall negative balance. The authors estimated cutaneous selenium losses to be about 140 to 200 mcg/day. Several studies have shown that plasma Se and GSHPx levels decline in both adults and pediatric burn patients [[142], [178], [130], [131]].

Because selenium is renally excreted, it is plausible that patients with impaired renal function may be at risk for toxicity. However, Shih et al. (2012) [180] reported no significant difference in serum Se at different stages of renal insufficiency in adults. However, literature is conflicting regarding TE status for renally impaired patients undergoing dialysis. Hemodialysis removes uremic toxins primarily by allowing equilibration of plasma and dialysate across a semipermeable membrane. The dialysate concentration of trace elements is not routinely equilibrated. Thus, substances that have lower concentrations in dialysate than in blood tend to be removed by dialysis. A meta-analysis of 128 studies conducted by Tonelli et al. (2009) [181] found that patients on hemodialysis had lower levels of selenium compared to the general population. However, the authors subsequently conducted their own study [182] of 200 Canadian hemodialysis patients and found that approximately 1.8% of study participants had low plasma Se levels. In contrast, Esmaeli & Rakshanzadeh, 2019 [73] found serum Se level was significantly lower in children undergoing hemodialysis and peritoneal dialysis compared to healthy children or in children with end-stage renal disease treated with conservative management. Thus, additional studies are needed to determine whether higher dosing is needed in patients with renal insufficiency who are on hemodialysis.

Preterm neonates may have increased selenium requirements and are thought to be at an increased risk for selenium deficiency for a number of reasons including limited stores created during shortened gestation, lengthened period of rapid growth, possibly decreased selenium adsorption in early neonatal period, increased selenium losses due immature kidneys (accretion rate of selenium of 1mcg/kg/day) [183] and associated clinical complications that often accompany prematurity and result in increased energy expenditure [184, 185]. Clinical determination of selenium status is also difficult in this patient population due to their complex clinical presentation, frequency of comorbid conditions, and lack of consistent correlation between clinical deficiency and Se levels. While biochemical determination of selenium status in preterm neonates has been reported to be potentially confounded by supplemental oxygen, steroids and acute illness [186, 187], comparisons to baseline status, preterm patients not on PN and term neonates on or off PN may still provide useful information. However, serum or plasma Se levels are thought to be more reflective of short-term selenium status compared to GSHPx activity. Existing literature suggests that a higher dose may be needed in the preterm population but is conflicting regarding the optimal dose of selenium supplementation. Therefore, additional studies may be helpful to better understand nutrient selenium parenteral requirements in preterm neonates.

8.1.6. Integrated Assessment of Effectiveness

To assess the efficacy of Selenious Acid Injection, the Applicant needed to demonstrate that the product adequately provided a supply of selenium as part of a parenteral nutrition regimen.

The Division finds the literature submitted by the Applicant to be adequate and in general alignment with the approach previously agreed upon prior to NDA submission. However, the submitted publications had several limitations including small sample size; heterogeneous

study population, dose studied, and efficacy and safety endpoints; and lack of control of confounders (e.g., enteral sources of selenium).

While none of the submitted trials were adequately designed and powered to establish clinical benefit. The clinical trials used in the assessment of effectiveness have primarily focused on measurement of selenium levels and GSHPx activity levels before and after intravenous supplementation of selenium in PN and have not routinely included clinical outcome assessments. However, the need to establish efficacy in the clinical trials for Selenious Acid Injection as a source of selenium for PN is not necessary because an increase and/or maintenance of serum or plasma selenium concentrations in patients administered PN containing selenious acid has been demonstrated across multiple studies. Measurement of Se levels before and after supplementation can be considered reasonably objective endpoints and therefore can distinguish the effect of selenium supplementation from spontaneous change due to the known natural course of a disease, a placebo effect or biased observations.

Lane et al. (1987) [3] conducted a controlled study that showed that parenteral selenium of 80 and 160 mcg/day increased selenium levels in 7 adult patients with underlying malabsorption on long-term PN in a dose-dependent manner. Sando et al. (1992) [4] showed in their controlled study that selenium levels fell with withdrawal of selenium supplementation of 200 mcg/day but rose back to within the referenced range in adult and 6 pediatric patients on long-term TPN. Additional supportive studies (primarily observational) in patients on PN reported a broad range of dosing (32 to 400 mcg/day) for parenteral selenium supplementation in adults on PN. In general, a dose range between 60 and 200 mcg/day was found to be sufficient to restore plasma Se levels to within the reference range.

Huston et al. (1991) [5] assessed the effect of parenteral selenium supplement on Se levels in VLBW neonates on TPN in a RCT and found that neonates that did not receive selenium supplementation had lower Se levels compared to neonates that did receive supplementation at the time enteral feeding was initiated. Daniels et al. (1996) also conducted a RCT that assessed the effect of selenium supplementation in preterm neonates and found that parenteral selenium of 3 mcg/kg/day was able to maintain plasma Se levels in preterm neonates on PN. Additional supportive studies in pediatric patients also showed parenteral selenium supplementation ranging from 2 to 7 mcg/kg/day was able to increase or maintain Se levels to reference range although most studies described patients with underlying clinical and or biochemical selenium deficiency.

Overall, the literature provides supportive evidence for the use of intravenous selenious acid as a source of selenium to patients who cannot receive adequate nutrition through oral/enteral intake through the Se levels. These trials were evaluated in conjunction with the generally accepted scientific knowledge of the role of selenium in maintaining health and preventing/treating the potential clinical effects of deficiency. Studies and case summaries that assessed selenium-deficiency conditions (e.g., cardiomyopathy, myopathy, nail changes) demonstrated the role of selenium in treating these conditions, thereby supporting adequate

daily intake of selenium in preventing these conditions and providing it as a supplement in PN in those unable to take daily enteral feeds.

Additionally, efficacy in clinical trials is supported by standard oral/enteral nutritional requirements (i.e., Recommended Dietary Allowance or Intake (RDA, RDI) values), relative bioavailability of parenteral to oral formulations, current clinical PN guidelines based on expert consensus, as well as the time and extent of use in clinical practice.

Therefore, the Division finds that there is substantial evidence to support the proposed indication for Selenious Acid Injection as a source of selenium for PN when oral or enteral nutrition is not possible, insufficient, or contraindicated.

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant did not conduct any studies to support the safety of the proposed indication. The safety review is based entirely on extensive time and extent of use, evidence in published studies and post-marketing data from the following sources:

- Publications identified by the Applicant based on (b) (4) literature review
- Additional publications identified based on DEPI review of available literature not included in the submission
- Published literature on overdose reported with oral selenium
- Post-marketing adverse event reports from the Applicant's database, the FDA Adverse Event Reporting System (FAERS) database, and the Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS) database

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant did not conduct any additional studies in support of the application, rather summarized information about adverse reactions from published literature to support the safety of this application.

Adults:

The Applicant submitted 58 publications reporting on 1460 adults exposed to parenteral selenium. Fifteen of these publications included safety information (Tables 1 and 2 in Applicant Submission Module 2.7.3 Summary of Clinical Safety for Adults).

The adult literature primarily studied two populations:

- 1) Studies evaluating moderate- to high-dose parenteral selenium in critically ill patients for short durations ranging from 5 to 14 days.
- 2) Studies evaluating parenteral selenium supplementation in patients on PN.

In the studies evaluating parenteral selenium supplementation ranging from 200 to 4000 mcg/day in critically ill patients, selenium was not intended as a replacement nutrient in patients on PN, but rather given either alone or in combination with other trace elements or vitamins to investigate their anti-inflammatory/antioxidant effects. Nine publications (515 patients exposed) reported on specific safety outcomes (described in further detail below) and 1 study included a general statement that stated no specific adverse events were observed in patients treated with selenium.

In studies evaluating parenteral selenium as a nutritional source, patients in these studies received parenteral selenium supplement for up to 8 years at doses of up to 60 mcg/day; 129 months at doses up to 200 mcg/day; and 4 months at 400 mcg/day in adults. Most studies did not include any safety information. Three publications included a general statement that no specific adverse events were observed.

Additionally, DEPI identified 9 publications that reported on safety outcomes not included in the NDA.

Pediatric Patients:

The Applicant submitted 14 publications reporting on 485 pediatric patients on PN exposed to parenteral selenium at doses between 1.5 and 7 mcg/kg/day. Duration of exposure was reported in six studies and ranged from 6 days to 12 months. Only 1 publication [165] reported on safety information in 268 low-birth-weight (less than 1500 g) infants randomized to receive parenteral selenium supplementation of 7 mcg/kg/day. The results of this study suggested an acceptable safety profile at this dose and are further discussed in Section 8.2.3. Additionally, DEPI identified 2 publications that reported on safety outcomes not included in the NDA.

8.2.3. Safety Results

In general, the published literature did not report significant adverse events in adult and pediatric age groups associated with use of selenium in PN at the proposed dose.

Adult Published Literature

Adverse events (AEs) were not consistently reported in published literature. Of the 9 studies that did report on safety of parenteral selenium in adults, key findings are summarized below:

- 5 publications [57, 113-115, 121] reported no significant difference in AEs or serious adverse events between patients that received Se supplementation and control populations
- Siriwardena et al. (2007) [114] reported a higher number of deaths in critically ill patients with acute pancreatitis (4 out of 22 patients) that were randomized to receive an antioxidant cocktail (selenium 1000 mcg + ascorbic acid + n-acetylcysteine) compared to placebo (0 out of 21 patients).
- Forceville et al. (2007) [115] reported a numerically higher rate of multiorgan failure in critically ill patients with severe sepsis that were randomized to receive selenium 4000 mcg/day (32%, N=31) compared to placebo (14%, N=29) but the difference was not statistically significant ($p=0.091$)
- Chelkeba et al. (2015) [120] reported early discontinuation in three patients (N=29) randomized to receive selenium 2000 mcg/day after 2 days of infusion due to rise in serum creatinine (values not reported).

Review of 9 additional publications not included in the NDA containing safety information revealed only 2 publications that specifically assessed for selenium related AEs. Reimund et al. (2000) [152] assessed TE status in patients and found the mean plasma Se level was low compared to controls (5.72 versus 7.39) but reported no symptoms suggestive of Se deficiency. Schmidt et al. (2018) [140] conducted a RCT to evaluate the effect of high dose selenium (4000 mcg on Day 1 followed by 1000 mcg/day IV for up to 13 days) versus placebo in post-cardiac surgery patients. Thirteen patients died during the observation period (8 in Se group and 5 in placebo group) attributed to cardiac failure leading to multiple organ dysfunction. None of the deaths were attributed to the study medication. The authors reported elevated mean whole blood Se levels reaching above the normal reference range (10.08 ± 1.73 mcg/dL) with the highest level reaching 19.68 mcg/dL. While the authors reported no clinical signs of acute selenium toxicity, a significant increase in serum bilirubin without evidence of hemolysis or liver failure was also reported (details not provided in publication). Elevated bilirubin has not been reported in other clinical trials of similar high doses and duration [57, 113, 115, 120, 122, 123]. There have been two case reports of patients who developed elevated bilirubin (Gasme et al. (1997) [10] and Civil et al. (1978) [188] in Appendix 15.14. Both patients ingested greater than 1 g of selenium and reported much higher plasma Se levels of 272 mcg/dL and 310 mcg/dL. The significance of the finding of elevated bilirubin is unclear given the high-risk population enrolled in this study. Furthermore, the safety findings reported in this study is of limited applicability to the proposed indication given the much higher selenium dosing.

Pediatric Published Literature

Darlow et al. (2000) [165] evaluated 268 very low birth weight neonates that received parenteral selenium at 7 mcg/kg/day when fed parenterally or 5 mcg/kg/day when fed enterally initiated within 1 week of life until 36 weeks' postmenstrual age or discharge home. No AEs consistent with signs and symptoms of selenium toxicity were noted by the investigators.

Etani et al. (2014) [189] evaluated Se levels in five patients (age range 2 to 20 years old) with intestinal dysfunction and/or neurological disabilities receiving PN and selenium supplementation ranging from 150 to 350 mcg/week (i.e., 21 to 50 mcg/day) for 12 months. Two patients (ages 5 and 20) developed transaminitis (values not reported) which the investigators attributed to intestinal failure associated liver disease and use of concomitant anti-convulsant drugs.

Review of 2 additional publications not included in the NDA did not yield additional safety information relating to parenteral selenium supplementation. In Dressler et al. (2018) [175], the effect of a ketogenic PN diet in 15 children with epilepsy which included TE was investigated. The amount of selenium supplementation was not specified, and selenium-related toxicities were not specifically assessed. In Smith et al. (2018) [172], investigators reported on their experience with a protocolized monitoring of children on HPN with TE supplementation. While two patients had reported abnormal values related to selenium and zinc (values were not specified), investigators reported no patients developed symptoms related to deficiency or toxicity. Selenium dosing and assay information were not provided thus it is difficult to draw any conclusions regarding safety of selenium supplementation from these 2 publications.

8.2.4. Additional Safety Information

Human Carcinogenicity or Tumor Development

No reports linking parenteral selenium to carcinogenicity were identified in the literature.

Human Reproduction and Pregnancy

The Division of Pediatric and Maternal Health (DPMH) was consulted to assist with evaluating the safety of parenteral selenium in pregnancy and lactation. Refer to DPMH labeling review (Carrie Ceresa, Pharm D and Miriam Dinatale, D.O) for additional details.

Briefly, published literature notes that pregnant women have an increased metabolic demand for trace elements, including selenium and that selenium deficiency is associated with adverse pregnancy (e.g., miscarriages) and fetal outcomes (e.g., low birth weight).

DPMH determined that the Applicant conducted an adequate review of the published literature regarding selenium exposure during pregnancy and lactation. In these studies, selenium supplementation was evaluated for a variety of reasons including reduction of pre-eclampsia risk in selenium-deficient pregnant women, effect on insulin resistance during pregnancy, reproductive outcomes, inflammation and oxidative stress during pregnancy. Overall, DPMH agrees with the Applicant's conclusion that selenium supplementation appears to be safe in healthy pregnant and lactating women.

Pediatrics and Assessment of Effects on Growth

There are no adequate and well-controlled studies of selenium supplementation and effects on growth. However, growth retardation has been reported in 1 study of 6 Japanese infants on PN with selenium deficiency (<4 mcg/dL) that improved with selenium supplementation [43].

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There are no reports of selenium abuse potential, withdrawal, or rebound.

Excess exposure to selenium can result in toxicity although the biochemical mechanism of selenium-induced toxicity has not been fully elucidated. Acute and chronic toxicity has not been reported in routine clinical use of parenteral selenium as a nutritional supplement or in short-term clinical trials with high-dose parenteral selenium for up to 4000 mcg/day. Overdose has been reported in intentional oral ingestions. In these patients, selenium concentrations are typically elevated but there appears to be no direct correlation between the extent of Se level elevation and the severity of symptoms.

Acute Oral Toxicity Effects:

Reports of acute fatal or near-fatal selenium poisoning with accidental or suicidal ingestion of selenium doses of greater than 1 gram/day has been reported and are summarized in Appendices 15.13 and 15.14.

Onset of nausea, vomiting, diarrhea, and abdominal pain within a few hours post-ingestion appear to be universal in patients presenting with acute selenium toxicity. Signs and symptoms of mild to moderate intoxication that did not result in death included myalgia, muscle spasms, irritability. Patients in these reports had selenium serum or blood concentrations in the range of 41 to 750 mcg/dL (see Appendix 15.14).

Death due to circulatory collapse and cardiopulmonary arrest has been reported after ingestion of greater than 5 grams of selenium in cases with known quantities of ingestion. In addition to severe gastrointestinal symptoms, “garlic” breath and altered mental status with progression to coma have been reported in these case reports (see Appendix 15.13).

In cases where Se levels were reported, fatal selenium poisoning has been reported at blood Se level as low as 190 mcg/dL. However, reports of full recovery without sequelae have occurred in patients with acute selenium poisoning with plasma and serum Se levels between 200 and 300 mcg/dL [10, 188], suggesting a lack of clear correlation between raised selenium levels and adverse outcomes; underlying clinical conditions may also influence outcomes in these situations.

Chronic Selenosis:

Limited data available in humans with chronic exposure to excessive amounts of selenium are derived from dietary exposure studies in seleniferous geographic regions [3 to 7 mg/day (3000 to 7000 mcg/day)] and patients exposed to misformulated oral supplements [1.6 to 255 mg/day (1600 to 255000 mcg/day)] (summarized in Appendix 15.15). The most frequently reported features of chronic selenium toxicity were alopecia and nail brittleness [7]. Other signs of toxicity include gastrointestinal disturbances, skin rash, garlic breath, fatigue, irritability, and nervous system abnormalities [7, 190-192].

Study of subjects with higher than normal selenium intake in a seleniferous area in the U.S. in 1 publication [11] suggested that physical findings characteristic of selenium toxicity were not present in subjects whose selenium intake was as high as 724 mcg/day. Studies of subjects with endemic intoxication in Enshi County of Hubei Province of China [7, 190] suggested that clinical signs and symptoms of selenosis including hair and nail changes, skin rash, neurological effects (e.g., peripheral neuropathy, convulsions), and elevated prothrombin time occurred at a blood selenium level of approximately 100 mcg/dL, corresponding to a selenium intake above 850 mcg/day. Using a safety factor of 2, the authors proposed a maximal daily safe selenium intake of 400 mcg/day. Prolonged prothrombin time or coagulopathy has not been reported with chronic selenosis. Elevated INR was reported in one case of acute overdose of selenium ingestion of unknown quantities resulting in Se level of 3000 mcg/dL and eventual death [9]. However, given the likely coexistence of metabolic derangements in the setting of severe gastrointestinal symptoms, a causal relationship cannot be clearly established between coagulopathy and selenium toxicity. Additionally, bleeding complications and increased prothrombin time have not been reported as adverse events in selenium supplementation studies or in high dose clinical studies where patients received up to 4000 mcg/day for 14 days. Therefore, it is unlikely that parenteral selenium supplementation will lead to coagulopathy or increased risk of bleeding at the proposed therapeutic dose.

The results from these studies conducted in China were the basis for the IOM established Tolerable Upper Limit (UL), No Observed Adverse Effect Level (NOAEL) and the Lowest Observed Adverse Effect Level (LOAEL) for selenium at 400, 800 and 913 mcg/day, respectively [13].

QT

A through QT study has not been conducted by the Applicant. Cardiac damage (myocardial degeneration) due to high dose selenium (about 100x normal human intake) has been observed in animal studies. However, there are no in vitro or nonclinical data evaluating the effect of selenium on cardiac repolarization.

During the NDA review, it was noted that cardiac arrhythmias (e.g., ventricular fibrillation) and QT prolongation was described in several case reports of acute severe oral selenium overdose (see Appendices 15.13 and 15.14). An information request was sent to the Applicant requesting additional data and analysis of the cases for the potential of selenium to delay ventricular repolarization.

The Applicant conducted a review of relevant literature and concluded that there is no evidence for correlation between QT prolongation with intravenous Selenious Acid Injection based on the following:

- No incident cases of QT prolongation were identified in the clinical studies submitted in the NDA which reported 5403 selenium case exposures
- In a 2008 study of a selenium toxicity outbreak in 10 states involving 201 cases, with a mean exposure of 41,749 mcg/day, there were no reported cases of QT prolongation [193].
- Case reports of patients with QT prolongation and cardiac arrhythmia were reported in the setting of acute intentional oral overdoses confounded by severe gastrointestinal symptoms, metabolic derangements, and concomitant medications. Therefore, a definitive causal relationship cannot be established.

In addition to the lack of evidence supporting parenteral selenium's effect on ventricular repolarization, Selenious Acid Injection will be prescribed for use only in controlled settings as a sterile injectable additive to parenteral nutrition. Therefore, an overdose of sufficient quantity of drug needed to produce toxicity is unlikely to occur in clinical practice.

Safety Concerns Identified Through Post-Market Experience

The Division of Pharmacovigilance I (DPV-I) was consulted to conduct a pharmacovigilance review and provide an analysis of all AEs associated with marketed unapproved Selenious Acid Injection or other selenium products in the FAERS database, CAERS database, the medical literature, and the Applicant's post-marketing surveillance database. A summary of the review is discussed below. Refer to complete review by Drs. Jamie Ridley Klucken, Lisa Harinstein, and Monica Muñoz for additional details.

The Applicant submitted 23 post-marketing adverse event reports from their own post-marketing surveillance database (January 2006 through 26 November 2018) with Selenium Injection, Multitrace-5 (MTE-5), or MTE-5 concentrate¹ given parenterally which contained 54 post-marketing adverse events. Of the 23 reports, 11 reported intravenous selenium as a suspect (n=9) or concomitant product (n=2) and 12 reported intravenous MTE-5 (n=9) or MTE-5 concentrate (n=3) as a suspect product. Based on review of the 23 adverse event reports, DPV-I

¹ According to drugs.com, each mL of MTE-5 solution for injection provides Zinc 1 mg, Copper 0.4 mg, Manganese 0.1 mg, Chromium 4 mcg, and Selenium 20 mcg. Each mL of MTE-5 concentrate for injection provides Zinc 5 mg, Copper 1 mg, Manganese 0.5 mg, Chromium 10 mcg, and Selenium 60 mcg.

concluded that none of the Applicant's reports were deemed possibly or probably related to intravenous selenium for the following reasons:

- Presence of confounders that precluded definitive determination of causality including concomitant medications, presence of other TPN components including other TEs and nutritional supplements, and underlying disease states.
- Missing information (e.g., no individual patient was described in the report, no specific adverse event reported) which significantly limited the interpretability of reports.

DPV-I additionally performed a search of the FAERS database for all reports through February 21, 2019, CAERS database for all reports through February 25, 2019, and medical literature for case reports through February 25, 2019. The resulting 90 FAERS reports and 47 CAERS reports were reviewed and findings were comparable to DPV-I's analysis of the reports submitted by the Applicant. DPV-I did not identify any case reports of adverse events associated with standard recommended doses of selenium in the medical literature. However, DPV-I identified three medical literature case reports in which patients received very high doses (2,500 mcg intravenously over 7 days; 200,000 mcg orally daily; 240,000 mcg orally daily) of selenium and experienced mild adverse events (e.g., gastrointestinal symptoms, paresthesia, alopecia, fingernail loss, signs of thyroid deficiency) that appeared to be reversible upon drug discontinuation. Therefore, there does not appear to be any post-marketing safety signals or adverse events with parenteral selenium supplementation at the proposed doses for approval after review of data submitted by the Applicant and retrieved in the FAERS database, CAERS database, and medical literature.

Expectations on Safety in the Post-Market Setting

There is substantial post-marketing experience in both adult and pediatric populations as well as patients with a broad range of underlying conditions (e.g., burns, post-surgery, critical illness, chronic malnutrition) based on the marketed, unapproved intravenous selenious acid alone or as a component in MTE-5 without reports of adverse events at the recommended dosage and up to 4000 mcg/day. Using the UL of oral selenium 400 mcg/day and NOAEL of 800 mcg/day, it can be estimated that the UL and NOAEL for parenteral selenium is approximately 280 mcg/day and 560 mcg/day respectively based on oral bioavailability. Thus, the safety margin for the proposed dose is large. Therefore, it is unlikely that new safety information, will arise post-marketing with Selenious Acid Injection when used as recommended for the approved indication.

Integrated Assessment of Safety

The assessment of safety for parenteral selenium as a source of an essential element is based entirely on published literature for adult and pediatric populations. Given that most studies which reported safety data were not intended to assess the safety of parenteral selenium as a nutritional supplementation, these publications can only serve to elucidate overt adverse

effects. Interpretation of available safety findings in the published literature that reported on AEs of patients receiving parenteral selenium is challenging for the following reasons:

- Studies in adults reporting safety information typically enrolled critically ill patients with intention to study anti-inflammatory and antioxidant role of high-dose selenium. Doses studied in critically ill patients were significantly higher (e.g., 500 to 4000 mcg/day in adults) than the recommended dosing of 60 mcg/day and thus observed AEs may not be applicable to the proposed lower dosing. In addition, critically ill patients have significant co-morbidity and a higher risk for mortality at baseline, which makes any conclusions about a causal relationship between parenteral selenium and the AEs observed difficult.
- The sample size across studies that reported on safety outcomes is relatively small. Seven of the 9 adult studies enrolled <50 patients per arm and only 2 studies [57, 121] enrolled greater than 100 patients in each arm (refer to Section 8.2.2 for the overall exposure).

Despite the paucity of safety information in published literature, it can be concluded that the margin of safety for dosing parenteral selenium as a source of nutritional TE requirements at the proposed dose of 60 mcg/day is wide based on the following observations:

- The IOM established an UL of 400 mcg/day, NOAEL of 800 mcg/day, and the LOAEL of 913 mcg/day for oral intake in adults based on chronic exposure to excessive levels of oral selenium.
- Unapproved but marketed parenteral selenium has been used in clinical practice for close to 30 years without reports of significant adverse events.
- No reports of significant adverse events in clinical studies attributed to parenteral selenium supplementation for up to 8 years at doses of up to 60 mcg/day, 129 months at doses up to 200 mcg/day, and 4 months at 400 mcg/day in adults.
- Studies and case summaries in pediatric patients on parenteral selenium supplementation between 14 days to 39 months reported no significant adverse events associated with parenteral selenium. The doses of selenium supplementation reported in these studies varied between 1.5 mg/kg/day to 7 mcg/kg/day.
- Reports of acute and chronic toxicities of oral selenium suggest that fatalities related to acute poisoning occur at doses greater than 5 grams while clinical signs and symptoms of chronic selenium toxicity have not been observed at oral ingestions below 800 mcg/day.
- There is no clear correlation between the amount of selenium ingested, severity of clinical presentation of toxicity and Se blood concentrations, although toxicity has not been observed in patients with plasma Se levels below 30 mcg/dL.

In summary, the published clinical experience and trials provide extensive safety experience on intravenous administration of selenious acid as an additive to PN in patients on long-term PN or administered as a high-dose (up to 4000 mcg/day) short-term infusion to various critically ill

patient populations who are not receiving PN, although with noted limitations. There has also been considerable post-marketing experience of marketed, unapproved parenteral selenium in a wide range of doses and patient populations across different age groups. Additionally, clinical studies and post-marketing reports have not conclusively identified selenium-related adverse reactions in patients receiving intravenously administered PN-solutions containing intravenous selenious acid within the recommended dosage range. Therefore, it can be concluded that there appears to be few, if any, adverse reactions within the recommended dose of 60 mcg/day.

8.3. Statistical Issues

Not applicable.

8.4. Summary of Dosing Recommendations

8.4.1. Applicant Proposed Dose

The Applicant has proposed a selenium dose of 60 mcg/day in adults. The Applicant proposed that dosing range is not necessary for adult patients because the dose can be individualized, and additional selenium supplementation can be added to meet a patient's changing needs.

The Applicant initially proposed a dose of [REDACTED] (b) (4)

[REDACTED] proposed dosing to 2 to 4 mcg/kg/day

Subsequently, the Applicant revised [REDACTED] (b) (4) pediatric population less than [REDACTED] (b) (4) kg [REDACTED] (b) (4)

Dosing was further revised to 2 to 4 mcg/kg/day in pediatric patients weighing less than 7 kg and 2 mcg/kg/day in pediatric patients weighting 7 kg and above, up to 60 mcg/day.

8.4.2. Dosing Considerations During Review

While there are uncertainties related to dosing to allow adequate selenium supplementation in patients relying on PN due to the limitations of Se levels and data from published literature (as discussed in Sections 8.1.1, 8.1.3, and 8.1.4), dosing for Selenious Acid Injection is supported by the following observations and published data:

Adults

- The estimated selenium intake in the adult U.S. diet is 111 mcg/day and in standard enteral formulas is 62 to 110 mcg. Therefore, selenium deficiency is unlikely in most

patients without underlying gastrointestinal conditions who require short-term PN support.

- Established oral RDA/RDI of 55 mcg/day in adults and 70 mcg/day in pregnant and lactating females.
- Assuming the bioavailability of oral selenium to be approximately 70%, it can be deduced that dosing for adults and pregnant/lactating females based on the RDI should receive a parenteral dose of approximately 39 mcg/day for adults and 49 mcg/day for pregnant/lactating females.
- UL of oral selenium 400 mcg/day and NOAEL of 800 mcg/day translating to 280 mcg/day and 560 mcg/day for parenteral selenium respectively based on oral bioavailability. Thus, the safety margin for the proposed dose is large.
- Published studies findings including:
 - Healthy controls have Se levels higher than patients on chronic PN (with and without selenium supplementation). Therefore, patients on long-term PN are at risk for deficiency and may need periodic monitoring of Se levels.
 - A broad range parenteral selenium doses between 32 to 400 mcg/day have been shown to provide a source of selenium sufficient to maintain or increase plasma Se levels to levels comparable to healthy controls, although the dose-response relationship is unclear. However, studies suggest that a proportion of chronic PN patients (who may have underlying deficiencies) receiving the Applicant's proposed dose of 60 mcg/day still had Se levels below the reference range.
 - No reports of serious adverse events attributed to parenteral selenium supplement in patients on chronic PN.

In summary, the average American adult is unlikely to have selenium deficiency based on data on dietary intake. In patients unable to obtain selenium via oral or enteral routes, data from published studies suggest a broad range of parenteral selenium dosing (32 to 400 mcg) was able to maintain Se levels within the referenced range in these patients. However, studies also suggest that doses less than the RDA/RDI of 60 mcg/day may be inadequate to meet the daily needs of some patients. The adequate dose of selenium supplementation is influenced by many factors which were not described or controlled for in these studies including underlying nutritional status, existing clinical condition(s), the availability of other sources of selenium, and Se level monitoring practices. Therefore, the Applicant's proposed dose of 60 mcg/day is anticipated to meet the needs of most patients and is well within the safety margin based on the UL and NOAEL. Additionally, product labelling will contain language informing prescribers dosing of parenteral selenium supplementation should be individualized as discussed above and periodic monitoring of Se levels should be considered in long-term TPN to prevent deficiency.

Pediatrics

- FDA requirement for infant formula to contain 2 to 7 mcg of selenium/100 kilocalories (21CFR107.100).
- Established oral RDA/RDI between 15 to 55 mcg/day.
- Human milk studies suggest that the estimated oral daily requirement in infants is 2 mcg/kg/day.
- UL of oral selenium between 45 to 400 mcg/day translating to 32 to 280 mcg/day in pediatric patients \leq 14 years old.
- Published studies findings including:
 - Prospective, RCT by Huston et al. (1991) suggested that parenteral selenium supplementation of 1.5 mcg/kg/day was not able to maintain blood Se assay levels in preterm neonates weighing less than 1000g.
 - Addition of selenium to PN in pediatric studies between 2 to 7 mcg/kg/day led to increases in Se levels although the dose-response relationship is unclear.
 - No reports of serious adverse events attributed to parenteral selenium supplement in neonatal or pediatric patients on chronic PN.

Because the RDI encompasses a wide pediatric age range recommending a single dose of 20 mcg/day for pediatric patients up to 4 years old, a weight-based dosing was estimated based on the RDA which offered narrower age bands (see Appendix 15.5). Using the RDA and the estimated bioavailability of oral selenium (70%), it can be estimated that a dose of 2 mcg/kg/day will meet the daily selenium needs for patients weighing 7 kg or more. In patients less than 7 kg, a dose of 4 mcg/kg/day is appropriate based on the same rationale.

During review cycle, the Applicant proposed a dose range of 2 to 4 mcg/kg/day in pediatric patients weighing less than 7 kg based on current clinical practice and expert consensus guidelines. Taking into consideration the labeling recommendation for prescribers to individualized dose based on the patient's clinical condition, the dosing recommendation proposed by the Applicant for pediatric patients appears to be reasonable (see Section 10 for detailed discussion on rationale for proposed pediatric dosing).

8.4.3. Dosing Recommendations

The Division's recommendations for dosing are outlined below in Table 12.

Table 12: Summary of Dosing Recommendations

Population	Selenium IV: Recommended Dose
Pediatric Patients <7 kg	2 to 4 mcg/kg/day
Pediatric Patients ≥ 7 kg	2 mcg/kg/day (up to 60 mcg/day)
Adults	60 mcg/day

Additionally, the Division concurs with the Applicant in their recommendation that dosing of Selenious Acid Injection should be individualized based on the patient's clinical condition, and nutritional requirements, as well as additional selenium supplementation from oral/enteral intake.

The proposed recommendations for Selenium Acid Injection dosing are also consistent with published guidelines from expert nutrition advisory groups and government organizations including the IOM and specialty societies for parenteral and enteral nutrition (e.g., ASPEN) that have developed dosing guidelines for essential trace elements in parenteral nutrition based on review of the available literature (Appendix 15.5).

8.5. Conclusions and Recommendations

The Applicant has submitted a literature-based 505(b)(2) NDA application for Selenious Acid Injection for use in adult and pediatric patients as source of selenium in PN when oral or enteral nutrition is not possible, insufficient or contraindicated.

Selenium is an essential TE obtained primarily through diet that is required to maintain human health. Selenious Acid Injection contains 60 mcg/mL of elemental selenium. Since 1984 selenium has been routinely added to PN solutions. Parenteral selenious acid products have been marketed unapproved since that time. This is the first selenious acid product that has been reviewed under an NDA.

The Applicant has not conducted any clinical trials of their product. They are relying on literature including randomized, placebo and active-controlled clinical trials in a range of patient populations (neonatal, pediatric, and adult), that primarily evaluate systemic concentrations of selenium in response to intravenous selenium supplementation in patients receiving PN. The relied upon literature describes parenteral selenium, the active ingredient obtained from selenious acid as well as selenite and in similar dose ranges as that proposed by the Applicant. In addition, the proposed intravenous dosing regimen of 60 mcg/day for adults aligns with the RDI (55 mcg/day for adults) for oral selenium, when accounting for the oral bioavailability (approximately 70%) of selenium and the bioavailability of IV selenium (presumed 100%).

Overall, the data supports the efficacy of 60 mcg/day in adults and 2- 4 mcg/kg/day in pediatric patients weighing less than 7 kg and 2 mcg/kg/day in pediatric patients weighing 7 kg or greater. (b) (4)

For the pediatric dosage rationale see Section 10 Pediatrics. This dosage is anticipated to meet the nutritional requirements of most patients on PN. However, the dosage must be individualized accounting for the patient's clinical condition, nutritional requirements, and other sources of selenium intake either orally or enterally. Some patients will have higher clinical requirements, most notably those on chronic PN. Therefore, in these types of patients to avoid clinical deficiency, periodic monitoring of systemic selenium concentrations, along with clinical examination, should be considered.

The safety database includes information from clinical trials and post-marketing adverse event reports of intravenous selenious acid at and above the recommended clinical dosage (range of 32 mcg to 400 mcg/day). Despite some limitations to the safety information available from clinical studies, due to lack of rigorous data collection and reporting, there appears to be few, if any, adverse reactions within the recommended dosage range. Published case reports of acute toxicity reported with overdose of oral selenium and chronic selenosis also inform the safety of the recommended intravenous dosage. Signs and symptoms of toxicity have been reported with acute and chronic oral doses at least 100-fold above the proposed intravenous dosage. The safety margin in adults is further supported by the oral selenium Tolerable Upper Limit (UL) of 400 mcg/day (approximately 280 mcg/day of intravenous selenious acid, based upon an oral bioavailability estimate of 70%).

In conclusion, the benefits of the proposed product outweigh the potential risks, and approval of Selenious Acid Injection in adults and pediatric patients for the proposed indication is recommended.

9. Advisory Committee Meeting and Other Consultations

9.1. Medical Policy & Program Review Council (MPPRC) (Feb. 27, 2019)

On Feb. 27, 2019, the Division sought the Council's comments and recommendations on the planned review approach for this 505(b)2 application.

The Council agreed with the Division that there is substantial evidence that selenium is a required TE for health maintenance and recognized the challenges in identifying the optimal parenteral dose and the uncertainties of dosing in special populations. The Council agreed with DGIEP's approach to approve the proposed Selenious Acid Injection product for the indication 'as a source of' selenium for PN in adult and pediatric patients based on collective evidence including clinical data on selenium supplementation in PN patients, known enteral nutritional requirements (e.g., Recommended Dietary Allowance, Reference Daily Intake (RDA, RDI)), relative bioavailability of oral versus intravenous administration, current clinical PN guidelines, the available toxicity data, as well as the time and extent of use in clinical practice. In addition, the Council recommended the Division consider a post marketing requirement (PMR) study or studies to obtain additional data to support dosing in populations where the evidence is scarce and suggestive of differential dosing.

9.2. Evaluation of Systematic Review of Medical Literature (Office of Surveillance and Epidemiology)

The Division of Epidemiology I (DEPI) assessed a systematic literature review submitted by the Applicant in support of NDA 209379. For details, please see the complete consult review filed in DARRTS by Drs. J. Weissfeld, P. Bright, and S.K. Sandhu on Mar. 12, 2019.

DEPI found that:

- The Applicant commissioned a systematic literature review, conducted by the (b) (4) and reported by the Applicant as stipulated by pre-NDA negotiations with DGIEP.
- (b) (4) identified 72 articles by systematic search for medical literature about patients given selenium parenterally or selenium status in patients on parenteral nutrition.
- The medical literature found by (b) (4) presented no evidence for toxicity or other serious adverse consequences from selenium when administered intravenously for parenteral nutrition at conventional doses.

Expanding the (b) (4) search strategy, DEPI identified 51 additional articles not captured by (b) (4). A DEPI review of these additional articles supported conclusions reached by the Applicant about the safety of selenium for parenteral nutrition.

10. Pediatrics

Pediatric approval of Selenious Acid Injection as a source of selenium in parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated in pediatric patients from birth to less than 17 years of age is supported by the following observations and published data:

- Selenium is an essential trace element required for the synthesis of selenoproteins involved in multiple important biochemical functions
- Selenium is primarily provided through the diet; therefore, in patients unable to tolerate enteral feeds, selenium must be provided parenterally to meet the nutritional needs
- There are well-described clinical conditions associated with selenium deficiency in pediatric patients (i.e., Keshan disease and Kashin-Beck disease) additionally, alopecia and growth retardation have been reported in infants with selenium deficiency, thereby demonstrating the importance of ensuring all pediatric patients receive adequate amounts of selenium to support body processes
- The IOM recognizes the importance of receiving adequate amounts of selenium enteraly and has established age-based reference standards for daily selenium intake for the full pediatric age range down to birth, including term neonates
- Published clinical guidelines from professional organizations have endorsed the use of selenium as a PN additive for over 30 years
- In intravenous formulation of selenious acid has been marketed unapproved for use as a source of selenium in PN in the pediatric population since 1990
- Addition of selenium to PN generally led to increases in blood selenium and GSHPx activity levels in pediatric patients with baseline low levels, although the dose-response

relationship is unclear. Oral and parenteral selenium exposure appear to be associated with a wide safety margin. There are no reports of serious adverse events associated with parenteral selenium in adult or pediatric populations despite the extensive time and extent of use.

As noted in Section 2.1.3, the IOM relied on the following evidence-based approaches to derive recommendations for daily selenium needs in pediatric patients: (1) measured selenium levels in human breast milk and mean volume of milk intake to estimate adequate selenium intake in children ages 0 to 12 months; and (2) data from adult intervention studies to derive estimates for children and adolescents ages 1 to 18 years (see Section 2.1.3) . The resulting RDA values recommended by the IOM estimate the average daily selenium intake needed to meet the nutritional requirements of nearly all (97% to 98%) healthy individuals. The RDI provides recommendations that include broader age bands than the RDA and are based on the highest RDA for the age groups within the respective age bands. While the RDI recommendations are intended to ensure the daily selenium needs of all ages are adequately met, RDI values encompass a wide pediatric age range that poses a challenge to developing a simplified weight-based dosing regimen for Selenious Acid Injection that would be appropriate for pediatric patients of all ages including those in the lower weight percentiles. The narrower age bands upon which the RDA values are based allow for more precise calculations to address this challenge while still addressing the daily selenium needs for up to 98% of individuals.

Pediatric dosing recommendations are therefore based on the following considerations:

- Because of the wide safety margin for toxicity, the priority is to ensure adequate dosing to meet the needs of the youngest, lightest-weight patients
- Conversion of the daily enteral selenium requirements outlined in the RDAs to parenteral requirements assumes that selenium is 70% orally bioavailable
- Pediatric populations receiving PN include critically ill and underweight patients who fall within lower- weight percentiles for age. Therefore, dosing recommendations should encompass these patients with outlying weights in addition to average-weight pediatric patients
- Weight-based dosing should span as many age bands as possible while providing adequate supplementation
- Proposed dosing should not exceed the UL converted to parenteral levels based on the assumption of 70% oral bioavailability
- Labeling will advise prescribers to individualize the dosing as needed based on the patient's requirements

See Table 13 outlining the calculations used to evaluate the applicant's proposed dosing recommendations.

Table 13: Calculated Parenteral Se Needs Based on Institute of Medicine Recommended Dietary Allowance

Age Group	IOM Enteral Recommendations (mcg/day)		Calculated Parenteral Se Needs Based on IOM RDA		
	RDA ¹ (Amount Bioavailable ²)	UL (Amount Bioavailable ⁵)	5th Percentile Weight ³ (mcg/kg)	50% Percentile Weight ⁴ (mcg/kg)	98% Percentile Weight ⁶ (mcg/day)
Pre-term	No IOM RDA for this subgroup				
0-6 months	15 (10.5)	45 (31.5)	4.13-1.56	3.03-1.29	8.9-<20.9
7-12 months	20 (14)	60 (42)	2.04-1.71	1.69-1.43	20.9-<25.5
1-3 years	20 (14)	90 (63)	1.66-1.18	1.39-0.99	25.5-<41.8
4-8 years	30 (21)	150 (105)	1.76-1.03	1.47-0.82	41.8-<85.6
9-13 years	40 (28)	280 (196)	1.36-0.81	1.08-0.61	85.6-<153.4
>14 years	55 (38.75)	400 (280)	1.12-0.79	0.84-0.63	153.7-194

Abbreviations: IOM = Institute of Medicine; RDA=Recommended Dietary Allowance; UL = tolerable upper intake level

¹ Institute of Medicine (U.S.) Panel on Dietary Antioxidants and Related Compounds. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academies Press; 2000.

² Calculated Based on 70% oral bioavailability of enteral RDA

³ Parenteral RDA divided by the 5th percentile of the age range per CDC growth charts

⁴ Parenteral RDA divided by the 50th percentile of the age range per CDC growth charts

⁵ Calculated based on 70% oral bioavailability of enteral UL

⁶ Calculated based on 2 mcg/kg/day for the 98th percentile of the age range

Source: Reviewer generated based on IOM RDA and UL values

Based on calculations summarized in Table 13, a weight-based parenteral dosing regimen of 2 mcg/kg/day for Selenious Acid Injection will provide daily selenium in micrograms that will meet the daily selenium needs for patients weighing 7 kg and will slightly exceed the proportion of the RDA for selenium estimated to be orally bioavailable in patients weighing greater than 7 kg. The range (0.3 to 1.3 mcg/kg/day) by which a 2 mcg/kg/day dosing regimen would exceed the RDA for selenium is well within the proportion of the UL for selenium estimated to be orally bioavailable and, therefore, does not raise safety concerns.

The same weight-based dosing scheme of 2 mcg/kg/day will result in provision of parenteral Se at doses in micrograms that fall short of the RDA equivalent for Se in the majority of patients weighing less than 7 kg, particularly those at lower weight percentiles. Only patients 1 month

of age and older who are at the 95th percentile for weight and patients 2 months of age and older who are at least at the 50th percentile for weight would receive the RDA equivalent of Se parenterally. See Table 14.

Table 14: Estimated Parenteral Se Dose Based on Weight Percentiles in Patients Weighing Less than 7 kg

Age	Weight	2 mcg/kg/day Parenteral Dose	RDA Equivalent
0 month			10.5 mcg
5 th percentile	2.5 kg	5 mcg	
50 th percentile	3.5 kg	7 mcg	
95 th percentile	4.3 kg	8.8 mcg	
1 month			
5 th percentile	3.4 kg	6.8 mcg	
50 th percentile	4.3 kg	8.6 mcg	
95th percentile	5.4 kg	10.8 mcg	
2 months			
5 th percentile	4.1 kg	8.2 mcg	
50th percentile	5.3 kg	10.6 mcg	
95th percentile	6.4 kg	12.8 mcg	
3 months			
5 th percentile	4.8 kg	9.6 mcg	
50th percentile	6 kg	12 mcg	
95th percentile	7.4 kg	14.8 mcg	

1. Based on CDC growth charts for males 0-36 months of age

Provision of a 4 mcg/kg/day parenteral dose, rather than a 2 mcg/kg/day dose, would provide a sufficient source of Se to meet the amount of the RDA estimated to be orally bioavailable for a neonate in the 5th percentile weighing approximately 2.5 kg.

Given the wide safety margin for parenteral Se, the priority should be to ensure dosing is adequate to meet the needs of all pediatric patients, particularly the youngest and lightest weight patients. Accounting for the dosing needs of patients who fall in the lower weight percentiles for age is important for this product because the anticipated target pediatric population requiring PN will be critically ill and underweight. RDA-derived parenteral Se dosing calculations are one component of this analysis; conflicting reports about the precise daily Se needs of neonates suggest there are other factors which may impact daily needs. These factors are not readily quantifiable. Longstanding clinical guidelines have recommended a lower daily parenteral Se dose (2 mcg/kg/day) rather than the RDA-derived value of 4 mcg/kg/day for use in the youngest pediatric patients including preterm neonates with provisions to increase parenteral Se based on individual patient needs. Time and extent of use with selenious acid based on this approach along with the lack of reports of selenium deficiency in neonates who received 2 mcg/kg/day supports the adequacy of a 2 mcg/kg/day starting parenteral Se dose in patients up to 3 months of age at lower weight percentiles.

Product labeling will convey a recommended dose of 2 to 4 mcg/kg/day for patients weighing less than 7 kg to allow dosing flexibility to prescribers to either target the RDA equivalent dose or to begin with a lower starting dose in this weight cohort. Product labeling will contain language informing prescribers that subsequent dosing in all patients may need to be individualized. The maximum pediatric daily starting dose should not exceed the proposed maximum daily adult starting dose of 60 mcg/day. These pediatric dosing recommendations align with the clinical guidelines for ASPEN (see section 15.5).

(b) (4)



Selenious Acid Injection would trigger the Pediatric Research Equity Act (PREA) as a new active ingredient not previously approved by FDA for the proposed indication. Therefore, the applicant must provide a pediatric assessment which addresses the entire pediatric population, which includes providing an age-appropriate formulation. (b) (4)



Because selenium is primarily excreted through the urine, the potential for increased exposures in patients with varying degrees of acute and chronic impairment in renal function exists. However, as stated in Section 6.2.2, available published data do not appear to substantiate this concern in adults or pediatric patients with varying degrees of CKD not on dialysis to justify renal dosing recommendations for this product. One possible explanation for this finding could be a compensatory increase in fecal selenium losses in these patients, but this has not been proven. However, both adults and pediatric patients requiring dialysis appear to have lower blood selenium levels regardless of dialysis modality.

One cross-sectional single-center study in Iran examined a single fasting serum level of selenium, in 200 children ages 5 years to 18 years; 63 patients on regular hemodialysis, 45 on long-term peritoneal dialysis, 14 with chronic kidney disease that was medically managed without dialysis, and 78 healthy children [73]. The authors found significantly lower serum selenium levels in patients on hemodialysis and peritoneal dialysis compared to patients with

CKD not on dialysis and to healthy children. However, the timing of the blood draw relative to dialysis, which could have affected the findings, was not described in the publication.

Interpretability of the findings are further confounded by the fact that the authors used a broad reference range for selenium (58 to 234 mcg/L) based on normal reference range for adults. Pediatric reference ranges for selenium levels appear to be narrower and age-dependent.

As noted in Section 5.5.5, the safety assessment of aluminum exposure with this product does not exceed the limit established for daily patient exposure from all potential sources of aluminum in a TPN admixture of 5 mcg/kg/day (21 CFR 201.323).

In accordance with the 2019 Pediatric Labeling Guidance, the Pediatric Use subsection must include a pediatric use statement or reasonable alternative statement when a drug is approved in pediatric patients for an indication that is the same as an approved indication in adults. Because this approval is not based on adequate and well-controlled studies, a use statement that conveys that Selenious Acid Injection is approved in the pediatric population, including neonates, for the proposed indication, in addition to a statement that describes that safety and dosing is based on clinical experience, would be appropriate. Additionally, the Pediatric Use subsection should highlight adverse reactions that occur at a different frequency or severity than in adults. Accordingly, labeling should describe the increased risk of aluminum toxicity in preterm neonates with a cross-reference to a more detailed description in the corresponding Warnings and Precautions subsection.

11.Labeling Recommendations

11.1. Prescription Drug Labeling

Highlights of final labeling negotiations with the Applicant include the following:

- The Applicant's original proposed Proprietary Name [REDACTED] ^{(b) (4)} was determined to be unacceptable by DMEPA due to [REDACTED] ^{(b) (4)}
[REDACTED] The Applicant subsequently withdrew the proprietary name and plan to market the product under the established name "Selenious Acid Injection".
- **Section 2 Dosage and Administration:** The drug product is supplied as a Pharmacy Bulk Package vial that is for admixing in PN. It is not for direct intravenous infusion. Therefore, information on preparation, administration, admixing, stability and storage of PN solutions containing selenious acid was included in this section. In addition to the recommended dosage, it is noted that dosing should be individualized based on patient's clinical condition and systemic selenium concentrations should be monitored. The range of selenium concentrations reported in healthy subjects in the U.S. is included with the recommendation that interpretation of individual patient results should be performed in the context of the current laboratory reference range.
- **Section 5 Warnings and Precautions:** This section was updated to include pertinent PN product class safety information including pulmonary vascular precipitates, vein damage and thrombosis, aluminum toxicity (as required by 21 CFR 201.323) and laboratory monitoring. It is noted that these subsections are not specifically applicable to the selenious acid component of PN but are more general class labeling language for PN solutions in general.
- **Section 6 Adverse Reactions:** The review did not identify any selenium-related adverse reactions reported in clinical studies or postmarketing reports in patients receiving intravenously administered PN-solutions containing selenious acid within the recommended dosage range. [REDACTED] ^{(b) (4)}
[REDACTED]
- **Section 7 Drug Interactions:** This section was not included as the Applicant was not able to identify any relevant information on drug interactions with selenious acid when administered in PN.
- **Section 8 Use in Specific Populations:**
 - Pregnancy, Lactation: These sections were written as per PLLR format and content using the nonclinical and clinical data described elsewhere in this review.

- Pediatric Use: The product is approved for use in the entire pediatric population (birth to less than 17 years) and the risk of aluminum toxicity in preterm infants is described.
- **Section 10 Overdose:** This section was updated to provide information on acute and chronic selenium toxicity based on literature of oral selenium, including corresponding systemic selenium concentrations in these subjects. The oral UL and NOAEL with the estimated oral bioavailability of selenium are also included.
- **Section 12 Clinical Pharmacology:** Limited information on the distribution and elimination of selenium is included.

(b) (4)



Please see the approved label for final agreed upon labeling.

12. Risk Evaluation and Mitigation Strategies (REMS)

The benefit-risk profile for Selenious Acid Injection is favorable, and any potential risks can be mitigated through product labeling (see Section 11). There are no additional risk management strategies required beyond the recommended labeling.

13. Postmarketing Requirements and Commitment

As discussed in Section 10, PREA PMR will be issued to the Applicant to provide an age appropriate formulation to ensure accurate dosing volumes of Selenious Acid Injection for pediatric patients weighing less than 7 kg.

14. Deputy Division Director (Acting) Comments

I concur with the reviewers that the benefits of Selenious Acid injection for intravenous use that provides selenium, an essential trace element required to maintain optimal human health outweigh the potential risks and recommend approval of NDA 209379 as a source of selenium in adult and pediatric patients for parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated.

Selenious Acid injection, a New Chemical Entity will provide 60 mcg/ml of elemental selenium. NDA 209379 was granted priority review due to drug-shortage issues. Currently, there are no other approved parenteral Selenious Acid products, however, 'Selenious Injection' containing 40 mcg/ml of elemental selenium has been marketed by the applicant as an unapproved product for more than 30 years for a similar 'source' indication as a supplement to Total Parenteral Nutrition (TPN). Selenious Acid is also marketed, unapproved by the Applicant in a fixed-combination trace element product together with other trace elements.

Background:

Selenium is currently (legally) marketed as an oral dietary supplement per 21 CFR 101.9 that provides its oral Reference Daily Intake (RDI) value, which is 55 mcg/day for adults. The RDI for selenium was previously set at 70 mcg/day for adults, however based on the 2016 Final Rule² – Food Labeling: Revision of the Nutrition and Supplement Facts Labels, the RDI for selenium was decreased to 55 mcg/day for adults. This decision was made based on consideration of the Recommended Daily Allowance (RDA) or Average Intake (AI) values set in the Institute of Medicine (IOM) Dietary Reference Intakes (DRI) reports that are US consensus reports. Quantitative intake recommendations from these reports were considered when establishing the RDIs. Currently, in the US, the average daily intake of selenium³ from various sources is estimated to be higher than RDI values and selenium deficiency is rare.

Efficacy:

For this literature-based NDA, the Applicant commissioned a Systematic Literature Review (SLR) that was conducted by the (b) (4) (b) (4). Based on discussions with the Agency, the focus of the SLR, intended to support the efficacy and safety of parenteral selenium, was demonstration of adequate selenium exposure from parenteral use of selenium in adult and pediatric populations receiving PN. A SLR of selenium exposures with the oral and enteral use of selenium was also performed to supplement the information available on the parenteral route. In addition, the bioavailability of the oral and intravenous formulations was taken into consideration.

² <https://www.federalregister.gov/documents/2016/05/27/2016-11867/food-labeling-revision-of-the-nutrition-and-supplement-facts-labels>.

³ <https://ods.od.nih.gov/factsheets/Selenium-HealthProfessional/>.

The efficacy assessment of Selenious Acid injection for the proposed 'source of selenium' indication was based on the following:

1. Generally accepted scientific knowledge of the role of selenium in maintaining health and preventing/treating clinical manifestations of deficiency. Studies that assessed selenium-deficiency conditions (e.g., cardiomyopathy, myopathy, nail changes) demonstrated the role of selenium in preventing/treating these conditions, thereby supporting the need for adequate daily intake of selenium and for providing it as a supplement in PN to patients unable to take daily enteral feeds. Essentially, these studies demonstrated the need to maintain selenium concentrations within normal reference ranges.
2. Literature reports of clinical trials, including the following adequate and well-controlled trials in adult and pediatric age groups that focused primarily on measurement of selenium levels before and after parenteral selenium administration in the PN and other settings:
 - Huston et al. (1991) [5] conducted a randomized, controlled trial in preterm infants, less than 1000 gm, where selenium levels were compared between patients randomized to receive selenium supplementation at 1.5 mcg/kg/day in PN versus those without.
 - Daniels et al. (1996) [6] conducted a randomized, controlled trial in preterm infants, less 2000 gm where selenium levels were compared between patients randomized to receive selenium supplementation at 3 mcg/kg/day in PN versus those without; selenium supplementation helped maintain plasma selenium levels.
 - Rannem et al. (1995) [112] conducted a randomized, placebo-controlled trial in severely selenium-deficient home parenteral nutrition (HPN) patients in which patients received iv selenium or placebo to evaluate effects of supplementation on selenium concentrations; iv selenium was able to maintain selenium concentrations.
 - Lane et al. (1987) [3] conducted a non-randomized, controlled trial in HPN patients that evaluated effects of increasing selenium doses on selenium concentrations and showed a dose-response.
 - Sando et al. (1992) [4] conducted a non-randomized, controlled trial in HPN patients evaluating various parameters that could be used to assess effects of selenium supplementation, withdrawal and reintroduction on selenium concentrations. Selenium concentrations increased with supplementation and declined during withdrawal.
 - Baptista (1984) [130] conducted a non-randomized, controlled trial in selenium-deficient HPN patients compared to healthy controls to evaluate effects of iv selenium and showed a dose-response.
 - Manzanares et al. (2010) [123] conducted a randomized, controlled trial in patients with Systemic Inflammatory Response Syndrome (SIRS) using high-dose selenium and showed that selenium concentrations increased in patients treated with selenium compared to controls.

- Angstwurm et al. (2007) [57] conducted a randomized, placebo-controlled, multi-center trial in which high doses of selenium were used in ICU patients and showed that selenium concentrations increased in patients treated with selenium compared to controls.
- Chelkeba et al. (2015) [120] conducted a randomized, controlled trial in which high-dose selenium was administered to patients with sepsis and showed that selenium concentrations increased in patients treated with selenium compared to controls.

Multiple studies that focused primarily on assessing selenium exposures after selenium administration in the PN setting used a range of selenium doses (32 to 400 mcg/day) and were able to show an increase and/or maintenance of selenium concentrations. These studies also showed that PN not supplemented with selenium, especially long-term PN, could lead to selenium deficiency. Additionally, in studies that focused on using high-dose parenteral selenium (up to 4000 mcg/day) to assess clinical outcomes in other settings, eg., ICU, SIRS, etc., the efficacy of selenium was unclear, however, increases in selenium concentrations were seen in such patients.

There were study limitations, however. For example, in some studies of patients on long-term PN, it was unclear if they had routinely received selenium supplementation at appropriate doses prior to study enrollment and if their levels were being monitored (See further discussion below). Also, literature data were of variable quality, largely uncontrolled, and dosing, safety and efficacy assessments were conducted in heterogeneous populations. A number of studies were conducted outside the US, and variations in normal selenium levels, perhaps influenced by food consumed and geographical variations in soil selenium content made assessment of results challenging. Variable parameters (serum/plasma selenium levels, RBC selenium levels, plasma glutathione peroxidase, etc.) were used to assess selenium levels; it is unclear if validated assays were used, and there was lack of consistency in defining normal selenium levels and reference ranges across various parameters. Despite these limitations, there was overlap in defining normal selenium reference ranges, and selenium levels were able to be used across studies to determine systemic exposures based on parenteral selenium administration and to assess selenium deficiency-related conditions.

Overall, studies, including adequate and well controlled studies across a range of populations in the PN and other settings were able to consistently show an increase or maintenance of selenium concentrations upon administration of parenteral selenium; this was considered objective evidence of efficacy for the 'source' indication for NDA 209,379.

3. The standard oral/enteral nutritional requirements for selenium, i.e., Recommended Daily Intake values of 55 mcg/day for adults and the bioavailability of oral selenium obtained from various food sources (plant, animal, supplements, etc.) expected to be approximately 70%, while the bioavailability of the proposed parenteral formulation assumed to be 100%.

4. Consideration of professional society guidelines, e.g., those from the American Society for Parenteral and Enteral Nutrition (ASPEN), that recommend routine addition of parenteral selenium to PN formulas for adult and pediatric patients.
5. Consideration of the time and extent of use of parenteral selenium (> 30 years) as a supplement to PN in clinical practice.

Thus, the totality of available data supports the finding of substantial evidence of effectiveness for the following indication: "Selenious Acid Injection is a trace element indicated in adult and pediatric patients as a source of selenium for parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated".

Dosing:

Pediatrics: The sponsor proposed doses of 2 to 4 mcg/kg/day in [REDACTED] (b) (4) pediatric patients weighing less than [REDACTED] (b) (4) kg, [REDACTED] (b) (4) mcg/kg/day in pediatric patients weighing between [REDACTED] (b) (4) kg, and 60 mcg/day in adults [REDACTED] (b) (4)

The DPMH (Division of Pediatric and Maternal Health) considered selenium RDAs, the bioavailability of oral (assumed to be 70%) and parenteral selenium formulations (assumed to be 100%), and the range of pediatric populations, including preterm and low-birth weight infants, and has proposed a dose of 2 mcg/kg/day for patients \geq 7 kg and 2 - 4 mcg/kg/day for patients < 7 kg after discussions with the sponsor. This dosing regimen appears to be appropriate; ASPEN as such recommends a dose of 2 mcg/kg/day for neonatal and pediatric PN patients.

Adults: The proposed dose of 60 mcg/day in adults appears to be appropriate, considering the oral RDI of 55 mcg/day; some patients may need higher doses based on clinical needs. It is also in keeping with ASPEN guidelines that recommend a dose of 60 -100 mcg/day of parenteral selenium for adult PN.

The primary reviewer has concluded that available data support the efficacy of the proposed dose for adults, i.e., 60 mcg/day of parenteral selenium and that this dose is expected to meet nutritional requirements of the majority of patients on PN. The dose will need to be individualized based on clinical needs and other sources of selenium, and some patients, for e.g., those on long-term TPN, may require higher doses. Routine monitoring of selenium levels in patients requiring long-term PN may prevent the occurrence of deficiencies.

The CDTL has recommended a dose of 60-100 mcg/day of parenteral selenium for the proposed indication based on current US dietary intakes of selenium, lower selenium levels in previously conducted studies in patients on long-term TPN and selenium requirements for such patients that may be higher.

Current US dietary selenium intake is high^{3,4}. Per 2003-2004 NHANES data, the mean serum selenium concentration in US adults is 13.67 mcg/dL with selenium levels in healthy adults ranging from 6 to 15 mcg/dL. Thus, the average population is not expected to be selenium-deficient at baseline and the 60 mcg/day dose of parenteral selenium that is aligned with the oral selenium RDI of 55 mcg/day should be adequate for supplementing most PN patients. Patients with underlying conditions that predispose them to increased losses, for e.g. gastrointestinal illnesses, or those on long-term PN, would require monitoring of their selenium levels with appropriate dose adjustment.

As discussed, in previously conducted studies dating from the 1980's and 1990's, in patients on long-term PN who had lower selenium levels, it is unclear if these patients were adequately supplemented with selenium prior to study enrollment and if their selenium levels were routinely monitored; in some patients, doses higher than 60-100 mcg/day were required to normalize selenium levels. The amount of selenium required likely depended upon the patient's underlying condition and their baseline selenium supplementation status. PN supplementation with trace elements has evolved over the years and there is more awareness about monitoring trace element levels and preventing deficiencies. Currently, selenium deficiency is very rarely reported in the US and Canada³; nevertheless, product labeling will recommend monitoring of selenium levels and dose adjustment to avoid selenium deficiencies.

Safety:

The safety profile for this literature-based NDA for parenteral selenium also considered the effects of oral selenium and was based on information from clinical trials that primarily assessed selenium exposures, adverse events reports, including those from the FAERS and CAERS databases, and years of use in clinical practice. Doses of intravenous selenium in clinical trials assessing selenium exposures spanned a range of 32 mcg to 400 mcg/day while doses in clinical trials that evaluated iv selenium in other settings, e.g., ICU, SIRS, etc., were as high as 4000 mcg/day. Notwithstanding limitations associated with assessment of safety based on literature data, there appear to be no serious adverse events associated with use of parenteral selenium at the proposed doses. Acute toxicity has been reported in the oral selenium overdose setting at selenium doses greater than 1 gram/day. The tolerable Upper Limit (UL) for oral selenium established by IOM (Institute of Medicine) is 400 mcg/day, which would approximate to 280 mcg/day of intravenous selenious acid, based upon an oral bioavailability estimate of 70%.

PMRs:

Given concerns associated with appropriate dispensing of low volume doses for pediatric age groups, the sponsor will be asked to develop an age-appropriate pediatric formulation for patients < 7 kg as part of a PREA PMR.

⁴ <http://americanutritionassociation.org/newsletter/what-selenium>

Conclusions:

Literature reports submitted under NDA 209379, which included adequate and well-controlled trials, demonstrated that parenteral selenium administration at the proposed doses in the PN setting was able to consistently result in increase or maintenance of selenium concentrations across adult and pediatric age groups and this was as such considered an objective evidence of efficacy. Literature also discussed the role of selenium in preventing and treating symptomatic selenium deficiency and the importance of monitoring and maintaining selenium concentrations within normal reference ranges, which are reflective of prevention of selenium deficiency. Thus, based on the well-established benefit of maintenance of normal selenium concentrations, it may be concluded that there is a large body of evidence which shows that low selenium levels lead to adverse clinical outcomes, such that maintaining a normal selenium level and/or restoring normal levels in adequate and well controlled studies was sufficient to accept selenium levels as a surrogate endpoint for full approval for NDA 209,379.

The assessment of substantial evidence of effectiveness for NDA 209379 was further supported by the RDA/RDI values for oral selenium, as well as the bioavailability information for oral and parenteral selenium formulations, both of which are in alignment. Lastly, the generally accepted scientific knowledge of the role of selenium in maintaining health and years of use in clinical practice was taken into consideration.

Overall, the totality of data provides substantial evidence of effectiveness per 21 CFR 314.126 for parenteral Selenious Acid for the proposed indication.

I have considered the viewpoints of the clinical review team and conclude that based on the totality of evidence, a dose of 60 mcg/day of parenteral selenium for adults should be adequate for supplementing PN. This dose is equivalent to the RDI for oral selenium. It is acknowledged that some patients may require higher doses based on clinical needs and the label will convey this, however, the dose required may be even higher than 100 mcg. The label will recommend that selenium concentrations be monitored and will include the range of selenium concentrations in healthy adults in the US to guide healthcare providers regarding levels below which insufficiency/deficiency may be noted and whether the current level of supplementation is adequate to meet their needs. The label will also provide the Tolerable Upper Limit for oral selenium which is 400 mcg/day, which relates largely to acute toxicity. Considering the approximate bioavailability of oral selenium, this would be equivalent to about 280 mcg/day of intravenous selenium; however, it is unlikely that acute toxicity would be seen in the PN setting.

The benefits of Selenious Acid injection outweigh potential risks, and I recommend approval of Selenious Acid injection as a source of selenium in adult and pediatric patients for supplementation in parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated.

15.Appendices

15.1. References

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15.2. Financial Disclosure

Not applicable.

15.3. Systemic Review Framework

- **Briefly (in a few paragraphs) summarize the prevailing rationale for adding each individual trace element (TE) to standard parenteral nutrition formulations**
 - *Include the best available evidence that this element is essential (animals/humans), mechanism of action, etc.*
 - *It is anticipated that some of this information may come from textbooks (and constitute general medical knowledge); therefore, it does not need to be extensively written/supported*
 - *This information can be used to write Section 12.1 Mechanism of Action of the label.*
- **Summarize the current ASPEN dosing recommendations in adults/pediatrics for each TE in relation to the proposed dosing for each TE**
 - *In a paragraph or two summarize the rationale and basis for the current ASPEN recommendations (2015) supported by primary literature references.*
 - *Discuss any changes to the ASPEN recommendations over time and include the primary literature references to support the more recent changes in the recommendations.*
 - *The recommendations for some of the elements (e.g., zinc) have not changed substantially since 1979. For zinc, provide more complete details as to etiology of the original recommendations.*
 - *If societal guidelines are available, other than ASPEN, provide a discussion on any points of uncertainty or controversy between the guidelines with regards to best practices.*
- **Summarize the evidence to support the proposed dosing for each TE in parenteral nutrition**
 - *One table for adults and a separate table for pediatrics. These tables would be in addition to the tables numbered 1 through 4 found in your systematic literature reviews.*
 - *Study design should focus on randomized controlled trials that look at each TE separately. However, other trials with multi-trace elements can be grouped by type and assessed accordingly.*
 - *Focus on studies that used TE measurement which is widely approved as accurate description of TE content, given that all TE content measurement are not accurate.*
 - *The unit of doses should be the same across studies to allow for easier interpretation and comparability of studies. For example, micromolar units may be used, but the preferred units are mg or mcg.*
 - *When providing the concentration of TE in whole blood/serum/plasma, specify the biologic matrix, provide units reported in the article and provide a conversion to the units used by U.S. laboratories, if different. For example, selenium is measured in serum and whole blood. Units include mcg/dL and micromol/L. Report concentration in mcg/dL. Include reference ranges, when available.*
 - *Include mention of whether patients were receiving TPN only, TPN plus oral feeds, or TPN with TE supplementation.*

- *The data presented in this table should allow the reviewer to understand all the relevant aspects of the publication, sufficient to permit an understanding of the study results/conclusions without rereading the entire publication.*
- *Use the tables to summarize information on IV administration of TE in TPN (i.e., from the systematic review);*
- *Supplement the SR data using evidence from other patient populations/routes of administration (e.g., oral) using the best available data and supported by primary literature references.*
- *Integrate the data in the tables with the other available evidence in a narrative for each TE that considers the totality of the evidence (max of 3-5 pages).*
- *As part of the summary, describe the quality of the efficacy data, strengths and weaknesses, how persuasive, what are the limitations? What are the uncertainties in the available evidence to support the proposed dosing regimen?*

Summary of Publications in Adults of Trace Element – According to the Efficacy Outcome Studied (i.e., Prevention of Deficiency (Maintenance), Development of Deficiency With Suboptimal Supplementation, or Deficiency That Responded to Supplementation)

Author/Year of Pub/reference #	Study design ¹	Study population ²	Dose(s) Duration of treatment Reason for TE supplementation Other co-administered TEs	Efficacy Outcome Include descriptive and/or quantitative information for any of the outcomes provided Specify clinical, laboratory ³ and/or radiological outcomes	Comments ⁴

¹ Study design to include design (RCT or other), number of patients on treatment, number on placebo (if applicable), primary disease.

² Study population to include demographics (age [mean ± SD], race, gender, country) and baseline characteristics (other comorbidities, pregnancy/lactation, renal impairment, hepatic impairment, elderly, etc.). Baseline TE concentrations (if available). Number of patients who discontinued.

³ Laboratory includes both standard chemistries as well as the concentrations of TE in biologic fluids (blood, serum, etc.) measured during and at the end of study.

⁴ The Comments column is a free text column to capture any other relevant information included in the publication.

Additional TE specific comments:

Copper

- Copper can be added as various salts. Specify the salt form in the table (e.g., copper chloride vs copper gluconate).
- **Identify clinical conditions, medical settings, or population subgroups that may require higher or lower doses of each TE for parenteral nutrition.**
 - *Briefly summarize what is known about the TE in Renal Impairment, Hepatic Impairment, Geriatric Use, and Pregnancy. This may involve integrating data from routes of administration other than IV.*
- **Describe toxicities or adverse events associated with each TE, when used for parenteral nutrition.**
 - *One table for adults and a separate table for pediatrics.*

- *See comments pertaining to Efficacy table above.*
- *Integrate the data in the tables with the other available evidence in a narrative for each TE that considers the totality of the evidence (max of 3-5 pages).*
- *As part of the summary, describe the quality of the safety data, strengths and weaknesses, how persuasive, what are the limitations? What are the uncertainties in the available evidence to support the proposed dosing regimen?*

Summary of Publications of Trace Element – According to Safety or Toxicity Outcome Reported

<i>Author/Year of Pub/reference #</i>	<i>Study design¹</i>	<i>Study population²</i>	<i>Dose(s) Duration of treatment Reason for TE supplementation Other co- administered TEs</i>	<i>Safety Outcome Include descriptive and/or quantitative information for any of the outcomes provided Specify clinical, laboratory³ and/or radiological outcomes</i>	<i>Comments⁴</i>

¹ Study design to include design (RCT or other), number of patients on treatment, number on placebo (if applicable), primary disease.

² Study population to include demographics (age [mean ± SD], race, gender, country) and baseline characteristics (other comorbidities, pregnancy/lactation, renal impairment, hepatic impairment, elderly, etc.). Baseline TE concentrations (if available). Number of patients who discontinued.

³ Laboratory includes both standard chemistries as well as the concentrations of TE in biologic fluids (blood, serum, etc.) measured during and at the end of study.

⁴ The Comments column is a free text column to capture any other relevant information included in the publication.

• **Overall Risk/Benefit Assessment**

- *Using the available evidence and any uncertainties about the quality/strength of the evidence presented above, do the data support adding the trace element to total parenteral nutrition to support the adult/pediatric indication of “maintaining serum levels” of each TE?*
- *Consider the risk of deficiency versus toxicity for each TE. Which drives the overall assessment?*

15.4. Summary Recommendations From Consensus Groups and Guidelines on Selenium Nutritional Supplement

Table 15: Summary Recommendations From Consensus Groups and Guidelines on Selenium Nutritional Supplement

Age Group	IOM RDA ¹ (Enteral)	IOM UL ¹ (Enteral)	21 CFR 101 ² RDI	ASPEN ^{3,4} (1998, 2004) (Parenteral)	ASPEN (2012) ⁵ (Parenteral)	ESPGHAN/ESPEN/ESPR/CSPEN ⁶ (Parenteral)
<i>Pre-term</i>				Pre-term Neonates 1.5 to 4 mcg/kg/day		7 mcg/kg/day
<i>0-1 month</i>	15 mcg/day	45 mcg/day		Term Neonates 2 mcg/kg/day		
<i>1-6 months</i>				Premature Infants 2 to 3 mcg/kg/day		
<i>7-12 months</i>	20 mcg/day	60 mcg/day	20 mcg/day	Infants 1 to 3 mcg/kg/day (Max 100 mcg/day)	2 mcg/kg/day	2 to 3 mcg/kg/day (max 100 mcg/day)
<i>1-3 years</i>	20 mcg/day	90 mcg/day		1 to 3 mcg/kg/day (max 100 mcg/day)		
<i>4-8 years</i>	30 mcg/day	150 mcg/day				
<i>9-13 years</i>	40 mcg/day	280 mcg/day	55 mcg/day			
<i>14 - 18 years</i>	55 mcg/day					
<i>>18 years</i>						
<i>Lactation</i>	60 mcg/day		400 mcg/day	20 to 60 mcg/day	60 to 100 mcg/day	
<i>Pregnancy</i>	70 mcg/day			70 mcg/day		

Abbreviations: ASPEN = American Society for Parenteral and Enteral Nutrition; CSPEN = Chinese Society of Parenteral and Enteral Nutrition; ESPEN = European Society for Clinical Nutrition and Metabolism; ESPGHAN = European Society for Pediatric Gastroenterology Hepatology and Nutrition; ESPR = European Society for Pediatric Research; IOM = Institute of Medicine; RDA=Recommended Dietary Allowance; RDI=Reference Daily Intake; UL = tolerable upper intake level

¹ Institute of Medicine (U.S.) Panel on Dietary Antioxidants and Related Compounds. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academies Press; 2000.

² Office of the Federal Register. Code of Federal Regulations Title 21 - FDA. In: FDA[®] US, editor.: Government Publishing Office; 2016. p. 33.

³ Greene HL, Hambidge KM, Schanler R, Tsang RC. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition. Am J Clin Nutr. 1988;48(5):1324-42.

⁴ Mirtallo J, Canada T, Johnson D, Kumpf V, Petersen C, Sacks G, et al. Safe practices for parenteral nutrition. JPEN Journal of parenteral and enteral nutrition. 2004;28(6):S39-70.

⁵ Vanek VW, Borum P, Buchman A, Fessler TA, Howard L, Jeejeebhoy K, et al. A.S.P.E.N. position paper: recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. Nutrition in clinical practice: official publication of the American Society for Parenteral and Enteral Nutrition. 2012;27(4):440-91.

⁶ Domellöf M, Szitanyi P, Simchowitz V, Franz A, Mimouni F, Braegger C, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Iron and trace minerals. Clinical Nutrition. 2018;37(6):2354-9.

15.5. Data for Dose-Plasma Selenium Concentration Analysis

Table 16: Data for Dose-Plasma Selenium Concentration Analysis

Literatures	Dose Regimen (Intravenous Injection)	Patient Number (N)	Maintenance Dose Duration	Plasma Selenium Concentration (mcg/dL)
Angstwurm (2007) [57]	1000 mcg/day	Treated 116 Control 122	14 days	Median concentration after treatment: 2.05 μ M (16.17 mcg/dL)
Angstwurm (2004) [118]	500 mcg/day for 3 days 250 mcg/day for 3 days 125 mcg/day for 3 days	Treated 20 Control 21	3 days	Concentration after treatment: 7.9 \pm 0.6 mcg/dL
Berger (2001) [119]	500 mcg/day	Treated 20 Control 11	5 days	Day 1: 5.53, Day 2: 5.53, Day 5: 10.26, Day 10: 12.63, Day 20: 11.05
Valenta (2011) [122]	1000 mcg/day on Day 1 500 mcg/day on subsequent days	Treated 75 Control 75	14 days	Day 0: 3.32, Day 1: 5.29, Day 3: 7.18, Day 5: 9.24, Day 7: 10.58, Day 10: 11.37, Day 14: 10.50
Manzanares (2010) [123]	High dose: 2000 mcg dose over 2 hours, followed by 1600 mcg/day as a continuous infusion for 10 days Low dose: 1200 mcg dose over 2 hours, followed by 800 mcg/day as a continuous infusion for 10 days	Treated (high) 10 Treated (low) 10 Control 10	10 days	High dose Day 0: 2.31, Day 1: 3.82, Day 2: 5.02, Day 3: 5.32 Day 7: 6.03, Day 10: 8.74 Low dose: Day 0: 2.91, Day 1: 4.02, Day 2: 4.82, Day 3: 5.02 Day 7: 4.72, Day 10: 8.04
Mishra (2007) [124]	High Dose: 474 mcg/day for first 3 days, followed by 316 mcg/day and 158 mcg/day for 3 days each, and 31.6 mcg/day thereafter or Low dose: 31.6 mcg/day	Treated (high) 18 Treated (low) 22	14 days	High dose: Day 0: 4.98, Day 3: 12.24, Day 7: 12.40, Day 14: 11.06 Low dose: Day 0: 5.69, Day 3: 5.76, Day 7: 7.19, Day 14: 9.56
Berger (1998) [125]	High dose: 231 mcg Low dose: 33 mcg	Treated (high) 10 Treated (low) 10	8 days	High dose: Day 0: 5.53, Day 1: 5.92, Day 5: 5.53, Day 10: 6.32 Day 15: 6.32, Day 20: 6.32 Low dose: Day 0: 3.55, Day 1: 3.95, Day 5: 5.53, Day 10: 4.74 Day 15: 6.32, Day 20: 5.53
Lemoyne (1988) [132]	Patients received selenium (as sodium selenite) 118.5 mcg/day IV (9 patients). Two patients had no oral intake, 4 had	Treated 9 Control 10	1 to 180 months	Mean concentration after treatment: 13.39 mcg/dL

Literatures	Dose Regimen (Intravenous Injection)	Patient Number (N)	Maintenance Dose Duration	Plasma Selenium Concentration (mcg/dL)
	slight intake, and 3 had moderate intake. (home TPN patients)			
Baptista (1984a) [131]	Patients had been maintained on HPN for a mean of 36 months (13 patients). 32 mcg/day. Twelve of the 13 patients were receiving oral feeds. Controls were healthy volunteers	Treated 13 Control 12	38 months	Mean concentration after treatment: 7.26 mcg/dL
Baptista (1984b) [130]	Patients had been maintained on a selenium deficient TPN solution for a mean of 44 months, 78 mcg/day.	Treated 8 Control 10	44 months	Mean concentration after treatment: 8.99 mcg/dL
Btaiche (2011) [63]	69.14 mcg/day	Treated 24	40, 493 days	Mean concentration after treatment: 7.02 mcg/dL
Alfieri (1998) [194]	120 mcg/day	Treated 40	15.8 days	Mean concentration after treatment: 10.49 mcg/dL
Sando (1992) [4]	200 mcg/day	Treated 6	84 days	Mean concentration after treatment: 11.84 mcg/dL
Malone (1989) [195]	265.44 mcg/day	Treated 24	28.1 months	Mean concentration after treatment: 6.47 mcg/dL

Source: Reviewer Generated Based on Submitted Literature

15.6. Summary of Adult Reference Range of Selenium Assays in Literature

Table 17: Summary of Adult Reference Range of Selenium Assays in Literature

Selenium Assay	Reference: 1 st Author (Year)	Geographic Location	Reference Range
Whole Blood Se	Schmidt (2018) [140]	United States	10.08±1.73 mcg/dL
	Stoppe (2013) [196]	Germany	10 – 14 mcg/dL
	Angstwurm (2007) [57]	Germany	7.58 – 14.06 mcg/dL
Serum/Plasma Se	Uzzan (2017) [135]	France	7.11 – 11.9 mcg/dL
	Salota (2016) [108]	United Kingdom	7.11 – 12 mcg/dL
	Stoppe (2013) [196]	Germany	8-12 mcg/dL
	Btaichi (2011) [63]	United States	9.5 – 16.5 mcg/dL
	Valenta (2011) [122]	Prague	4.6 – 14.3 mcg/dL
	Angstwurm (2007) [57]	Germany	5.71-10.55 mcg/dL
	Heyland (2007) [100]	Canada	10-16.5 mcg/dL
	Angstwurm (2004) [118]	Germany	7 – 14 mcg/dL
	Berger (2001) [119]	Switzerland	6.3-12.2 mcg/dL
	Reimund (2000) [152]	France	5 – 10 mcg/dL
	Alfieri (1998) [194]	Canada	10 – 14.4 mcg/dL
	Berger (1998) [125]	Switzerland	5.5 - 14.2 mcg/dL
	Forbes (1997) [69]	United Kingdom	5.53 – 12.64 mcg/dL
	Buchman (1994) [45]	United States	9.5 – 16.5 mcg/dL
RBC Se	Rannem (1993) [127], (1995) [112]	Denmark	5.9 – 14.7 mcg/dL
	Berger (1992) [197]	Switzerland	7 – 10 mcg/dL
	Malone (1989) [195]	United Kingdom	6.3-15.3 mcg/dL
	Shenkin (1986) [198]	United Kingdom	6.32 – 15.8 mcg/dL
Whole Blood GSHPx	Rannem (1995) [112]	Denmark	3.1 – 6.2 U/L
	Malone (1989) [195]	United Kingdom	13 – 45 U/L
Serum GSHPx	Valenta (2011) [122]	Prague	4,170 – 10,880 U/L
Plasma GSHPx	Manzanares (2010) [123]	Uruguay	570 – 870 U/L
	Berger (1992) [197]	Switzerland	350 – 450 U/L
RBC GSHPx	Angstwurm (2007) [57]	Germany	96-150 U/L
	Rannem (1995) [112]	Denmark	217 – 504 U/L

Abbreviations: GSHPx = glutathione peroxidase; Hb = hemoglobin; RBC = red blood cell; U/L = units per liter

Note: The various but overlapped reference ranges of serum/plasma Se concentration reflect the various settings of bioanalytical method (atomic absorption spectroscopy) and sample preparation procedures.
 Source: Reviewer Generated Based on Submitted Literature

15.7. Summary of Pediatric Reference Range of Selenium Assays in Literature

Table 18: Summary of Pediatric Reference Range of Selenium Assays in Literature

Selenium Assay	Reference: 1 st Author (Year)	Geographic Location	Age Range	Reference Range
Serum/Plasma Se	Neelis (2018) [173]	Netherlands	Not specified	6.3 – 14.2 mcg/dL
	Johnsen (2017) [97]	United States	Not specified	2.3 – 19 mcg/dL
	Chen (2016) [169]	United States	0 to 2 months	4.5 – 9 mcg/dL
			3 to 6 months	5 – 12 mcg/dL
			7 to 9 months	6 – 12 mcg/dL
			10 to 12 months	7 – 13 mcg/dL
			Yang (2011) [171]	Not specified 2.3 – 10 mcg/dL
	Muntau (2002) [104]	Germany	< 1 month	1.5 – 10.66 mcg/dL
			1-2 months	1.5 – 10.03 mcg/dL
			2-4 months	1.03 – 9.32 mcg/dL
			4-12 months	1.34 – 11.61 mcg/dL
			1-5 years	3.4 – 12.88 mcg/dL
			5-18 years	4.19 – 12.40 mcg/dL
	Glauser (1999) [199]	United States	1-18 years	10.6 ± 1.8 mcg/dL (mean ± 1 SD)
	Lockitch (1989)[102]	Canada	Neonates (<72 hrs)	Birth weight: <ul style="list-style-type: none"> • <1500 g: 3.7 – 10.3 mcg/dL • 1500 to 2499 g: 4.7 – 13.4 mcg/dL • ≥2500 g: 5.4 – 15.6 mcg/dL
Plasma GSHPx	Lockitch (1989)[102]	Canada	Neonates (<72 hrs)	Birth weight: <ul style="list-style-type: none"> • <1500 g: 108 – 216 U/L • 1500 to 2499 g: 137 – 430 U/L • ≥2500 g: 155 – 925 U/L

Abbreviations: SD = standard deviation

Source: Reviewer Generated Based on Review of Submitted Literature

15.8. Summary of Observational Studies Evaluating Parenteral Selenium in Primarily Adults

Table 19: Summary of Observational Studies Evaluating Parenteral Selenium in Primarily Adults

First Author, Year, Location	Study Objective	Patient Population Number of Patients Females/Males Age	Trace Element Administration	Reported Findings	Comments
Uzzan et al. [135]* 2017 France	To evaluate the prevalence of low TE in patients on chronic PN.	Patients with chronic intestinal failure (defined as need of parenteral support (energy and/or intravenous fluid requirement) at least 8 times a month) and on PN with TE supplement for at least 3 months. N=73 <ul style="list-style-type: none">Mean PN duration was 8.9 years.Mean PN infusion frequency was 4.8±1.8 days per week.	<ul style="list-style-type: none">Sodium selenite 64.08±46.2 mcg/dayAdditional selenium supplementation was allowed as needed	<ul style="list-style-type: none">Mean serum Se was 8.93±2.37 mcg/dL.16 (21.9%) of patients had serum Se levels below the reference range (7.11 – 11.85 mcg/dL).No overt clinical manifestations of TE deficiency were noted.	<ul style="list-style-type: none">Broad range of selenium supplementation.Close to 22% of patients on chronic PN had serum Se levels below the reference range although not symptomatic.
Btaiche et al. [63] 2011 United States	To evaluate parenteral TE dosing, serum TE concentrations, and the frequency of serum TE monitoring in patients who received long-term home PN (>1 year).	Adult and adolescent >40 kg patients on HPN for at least 1 year: <ul style="list-style-type: none">N=26 (24 adults)19F/7MAge range: 14–72 years	Mean (standard error) daily dose: <ul style="list-style-type: none">Se 69.14 (2.56) mcgZinc 7.65 (0.74) mgCopper 0.99 (0.03) mgManganese 0.47 (0.10) mg	<ul style="list-style-type: none">Mean dose of Se was 69.14±2.56 mcg/day115 Se levels measuredMean serum Se was 10.1 mcg/dL; range: 5.45 to 14.39(RR: 9.5-16.5 mcg/dL)<ul style="list-style-type: none">44(38.2%) below RR69 (60%) within RR2 (1.8%) above RRNo symptoms of selenium deficiency were documented	<ul style="list-style-type: none">38% of patients did not meet nutritional requirements, as evidenced by Se levels below RR, at an IV Se dose of 69 mcg/day. While this suggest a biochemical deficiency, the clinical significance of this effect is unknown.

First Author, Year, Location	Study Objective	Patient Population Number of Patients Females/Males Age	Trace Element Administration	Reported Findings	Comments
Hatanaka et al. [153]* 2000 Japan	To investigated changes in serum and red cell Se levels and glutathione GSHPx activity in addition to urinary excretion of Se in patients receiving long-term PN with and without selenium supplementation	Adult and pediatric patients on long-term TPN: Adults (>15 years old): N=49 Pediatric (<15 years old): N=6 On PN for 1 to 192 months; enteral diet was not reported	PN + Sodium selenite (100-200 mcg/day): N=5 PN: N=50 Healthy and no TPN control: N=32	<ul style="list-style-type: none"> Serum Se were below the lower limit of controls (RR: 14 ± 4.35 mcg/dL) in 58% of patient who received PN for <1 month (19 out of 33) and 100% of patients who received PN for more than 3 months (n=20). Similar effects seen in RBC Se and serum GSHPx but less so for RBC GSHPx. Marked decreases in RBC GSHPx were observed in patients on PN for >6 months. Urinary Se increased in patients receiving parenteral Se supplementation (despite low serum Se levels) compared to those that did not. 	<ul style="list-style-type: none"> Increase duration of PN was associated with increased proportion of patients with serum Se levels below the RR suggesting that patients on long-term PN are at risk for selenium deficiency compared to those on short-term PN. RBC GSHPx activity levels may be not be affected for up to 6 months in patients on PN without selenium supplementation. Increased urinary excretion in patients receiving parenteral sodium selenite supplementation despite low serum Se levels.

First Author, Year, Location	Study Objective	Patient Population Number of Patients Females/Males Age	Trace Element Administration	Reported Findings	Comments
Reimund et al. [152]* 2000 France	To analyze TE status of HPN patients and compare them to inflammatory markers and clinical outcomes.	<p>Patients on HPN for various bowel conditions (e.g., short bowel, radiation enteritis, Crohn's disease, mesenteric ischemia)</p> <p>HPN:</p> <ul style="list-style-type: none"> • N=22 • Mean age: 52.7 ± 15.4 years (range 26 and 75) • Mean duration of HPN: 18.5 ± 31.9 months (range 1 and 132) • All patients received HPN infusion overnight <p>Controls:</p> <ul style="list-style-type: none"> • N=14 • Age and sex matched 	<p>Mean daily Selenium supplement:</p> <ul style="list-style-type: none"> • Females: 43.22 ± 16 mcg/day • Males: 66.35 ± 33.5 mcg/day 	<ul style="list-style-type: none"> • Patients on PN showed significantly lower levels of mean plasma selenium compared to healthy controls (5.72 ± 2.02 versus 7.49 ± 1.58 mcg/dL) but still within the normal range (5 to 10 mcg/dL). • Clinical examination found no signs of selenium deficiency. • Vitamin and mineral status were not different between patients with catheter infection and those who did not. 	<ul style="list-style-type: none"> • Patients on PN with selenium supplement close to the recommended RDI showed lower plasma level than healthy controls. • While the mean plasma Se level was still within the lower referenced range, there was still a portion of patients who had levels outside the normal range (details were not reported) • The effect of oral intake was not described in these patients.

First Author, Year, Location	Study Objective	Patient Population Number of Patients Females/Males Age	Trace Element Administration	Reported Findings	Comments
Alfieri et al. [194] 1998 Canada	To determine the levels of serum selenium, and zinc in a patient admitted for surgery who would require TPN therapy.	Post-operative patients who received TPN: <ul style="list-style-type: none">• N=40• 21F/19M• Mean age: 61 years• Mean duration: 15.8 days	Standard trace element additives to TPN were: <ul style="list-style-type: none">• Se 120 mcg• Zinc 5 mg Patients with initially suboptimal Se were given additional Se (60 mcg).	<ul style="list-style-type: none">• 52.8% (19/36) of the patients had initial serum Se below the lower reference value (RR: 10.0 to 14.4 mcg/dL).• Despite additional supplementation, the selenium levels did not normalize in 34.5% (10/29) of the patients.• Assessment for symptoms of selenium deficiency was not reported.	<ul style="list-style-type: none">• The initial low serum Se status may be a reflection of the acute stressor or surgery rather than actual body Se store.• Post-operative patients may have factors pre-disposing to selenium deficiency (e.g., increased Se losses due to drains and/or blood loss) and thereby may require higher doses. Supplementation at a dose of 120 mcg/day was suboptimal for approximately one-third of post-operative patients.
Forbes & Forbes [69] 1997 United Kingdom	To document the incidence and nature of clinical micronutrient deficiency within their HPN program and relate these findings to the delivery of HPN and to serum concentrations of certain micronutrients.	Patients intestinal failure receiving HPN: <ul style="list-style-type: none">• N=49 (only 32 had Se levels)• 32F/17M• Mean age: 46 years (range 24 to 66)• Mean duration: 64 months.	Daily administration of trace elements additive to PN: <ul style="list-style-type: none">• Se 63 mcg• Zinc 7.8 mg• Copper 1.3 mg• Manganese 0.1 mg	<ul style="list-style-type: none">• Serum Se range: 1.58 to 11.85 mcg/dL.• Number of patients with serum Se levels below, within, above RR (5.53 to 12.64 mcg/dL)<ul style="list-style-type: none">◦ 5 (16%) below RR◦ 27 (84%) within RR◦ 0 (0%) above RR	<ul style="list-style-type: none">• Wide range of serum Se levels adds uncertainty to interpretation.• Based on this study, 16% of the UK patients on HPN would have low Se levels and may be susceptible to selenium deficiency.• Clinical evidence of micronutrient deficiency was identified in 16 patients (33%); however, unclear whether selenium deficiency was specifically identified for this retrospective medical record review.

First Author, Year, Location	Study Objective	Patient Population Number of Patients Females/Males Age	Trace Element Administration	Reported Findings	Comments
Buchman et al. [45] 1994 United States	To determine the incidence of low selenium levels in home TPN patients and whether excessive urinary selenium losses are the cause.	Patients receiving TPN (underlying condition not reported): <ul style="list-style-type: none">• N=28• 16F/12M• Mean age: 51 years (range: 21 to 79 years)• Mean duration: 8.3±4.4 years	Patients received Se 40 to 60 mcg/day daily in their TPN. This study notes that the RDA for selenium is weight based at 0.87 mcg/kg	<ul style="list-style-type: none"> • Mean serum Se: 7.29±1.22 mcg/dL (RR: 9.5 to 16.5 mcg/dL). • 21 patients (75%) had low serum Se levels. • Of patients with low serum Se levels, 15 (73%) had elevated urinary Se losses. • An additional 40 and 70 mcg/day restored most patients who low levels to within RR. • One patient with decreased renal function required 200 mcg to maintain plasma Se level and another patient on hemodialysis required 160 mcg to maintain levels. • There was no significant correlation between serum or urine Se levels and glomerular filtration rate or renal tubular function. • Symptoms of selenium deficiency were not reported or assessed in this study. 	<ul style="list-style-type: none"> • 75% of the patients receiving 40 to 60 mcg/day of Se supplementation in TPN still had serum Se levels below the RR. However, the exact dose of selenium supplementation was not reported, therefore it is uncertain if the mean serum Se level was skewed by the proportion of patients that received less than 60 mcg/day. However, a greater percentage of patients had lower levels compared to studies that only evaluated the 60 mcg/day dose. • Some patients receiving inorganic Se parenterally may have higher renal losses. • The significance of increased replacement requirement in one patient with decreased renal clearance is unclear since selenium is renally excreted. • Higher dosing is required to maintain Se levels in patients on hemodialysis, which is consistent with literature suggesting increased loss of selenium through dialysis filtrate.

First Author, Year, Location	Study Objective	Patient Population Number of Patients Females/Males Age	Trace Element Administration	Reported Findings	Comments
Cohen et al. [200] 1989 United States	To describe the biochemical, physiological, and clinical consequences of Se deficiency and repletion in five patients who had been on HPN for >2 years.	<p>Patients with short bowel syndrome or recurrent obstruction receiving HPN; 1 patient had minimal oral intake but the remaining had normal oral intake.</p> <ul style="list-style-type: none"> • N=5 • 1F/4M • Mean age: 57 years (range 20 to 75 years) • Mean time on HPN before selenium supplementation: 18.6 months 	<p>When patients became markedly deficient in plasma and red blood cell glutathione peroxidase, they received Se (as selenious acid) 400 mcg/day IV for 4 patients and 100 mcg/day for 1 patient.</p>	<ul style="list-style-type: none"> • At approximately 1 year on HPN, plasma and RBC GSHPx levels approached severely deficient (<15% of normal (<24 U/g)) in all patients. • Replacement of selenium resulted in normalization of plasma GSHPx within 1 to 2 weeks. • RBC GSHPx activity took 3 to 4 months to normalize. • 3 of the patients had "slightly decreased" muscle strength that resolved after selenium supplementation. 	<ul style="list-style-type: none"> • Very small study limits generalizability of results. • Study in patients who are likely deficient based on clinical symptoms of muscle weakness. • It was unclear which patient received 400 mcg/day. • Se 100 mcg/day normalized plasma and RBC GSHPx levels in the 1 patient who received this dose. • Plasma GSHPx appears to respond more readily to changes in Se intake compared to RBC GSHPx.

First Author, Year, Location	Study Objective	Patient Population Number of Patients Females/Males Age	Trace Element Administration	Reported Findings	Comments
Malone et al. [195] 1989 United Kingdom	To evaluate a new TE supplement preparation in patients requiring LT PN.	<p>Patients receiving HPN; most patients had some oral intake; frequency of PN infusion varied between 3 and 7 nights per week</p> <ul style="list-style-type: none"> • N=24 • 12F/12M • Mean age: 42 years (range 18 to 62 years) • Mean duration of PN + Se: 6 ± 2.8 months. 5 patients were on Se supplement of 265.44 mcg per week (≈ 38 mcg/day) before trial. 	<p>Mean supplement per week (≈ 26 mcg/day):</p> <ul style="list-style-type: none"> • Se: 182 mcg on-study • Zinc: 33.3 mg on-study • Copper: 6.2 mg on-study • Manganese: 1.4 mg on-study 	<ul style="list-style-type: none"> • Before Se supplement (note 5 patients already on supplementation prior to start of study): <ul style="list-style-type: none"> ◦ Mean serum Se: 4.3 ± 2.3 mcg/dL ◦ (RR: 6.32 to 15.8 mcg/dL) ◦ Mean RBC GSHPx: 8 ± 4.1 ◦ (RR: 13 to 45 U/g Hb) • After Se supplement: <ul style="list-style-type: none"> ◦ Mean serum Se: 6.5 ± 2.4 mcg/dL ◦ Mean RBC GSHPx: 12 ± 3.1 • Symptoms of selenium deficiency were not reported or assessed in this study. 	<ul style="list-style-type: none"> • The 5 patients that received Se supplementation week (≈ 38 mcg/day) prior to the study had baseline serum Se levels within the normal RR. • The serum selenium concentration prior to the study was below the RR (~ 0.55 mcmol) for the remaining 19 patients which includes patients on supplements. • Se 182 mcg/week increased mean serum Se to within RR. • Results suggest that a Se dose of 26 to 38 mcg/day may be sufficient to maintain serum Se levels in UK patients on PN with oral intake.

First Author, Year, Location	Study Objective	Patient Population Number of Patients Females/Males Age	Trace Element Administration	Reported Findings	Comments
Shenkin et al. [198] 1986 United Kingdom	To assess TE status in patients on HPN	Patients receiving HPN \geq 3 months; Most patients had some oral intake <ul style="list-style-type: none"> • N=57 • Sex and age not reported • Duration of IV nutrition ranged from 3 months to 4 years 	Patients received a variety of trace element supplements ranging from 60 to 118.5 mcg/day via oral and parenteral routes	<ul style="list-style-type: none"> • RR established based on 50 members of laboratory staff that was age and sex matched. • Patients who received a supplement that contained selenium 118.5 mcg/day had plasma Se within the RR: 6.32 to 15.8. • Patients who received no specific selenium supplementation had both low plasma Se and low RBC GSHPx. • One patient reported symptoms of muscle weakness that improved with Se supplement (details not provided). 	<ul style="list-style-type: none"> • Wide range of oral and parenteral selenium received. • All patients had improved levels. • Patients who received a supplement that contained selenium 118.5 mcg/day had plasma Se within the RR although investigators did not specify baseline levels or report a trend in levels overtime.
Néve et al. [201] 1986 Belgium	To report on the effect of selenium supplementation in patients with low Se status on Se assays	Patients with gastrointestinal disease or malnutrition and low Se status <ul style="list-style-type: none"> • N=10 • Sex and age not reported 	Patients received one or more of the following treatments: <ul style="list-style-type: none"> • Se (as sodium selenite) 130 to 150 mcg/day IV or 100 mcg (n=1) or 50 mcg (n=1) orally • Se (as DL-selenomethionine) 50 or 100 mcg/day orally or enterally (except given IV for 1 patient) 	<ul style="list-style-type: none"> • All patients had low Se levels at baseline. • All forms of selenium supplementation restored normal Se status of depleted patients. • Symptoms of selenium deficiency were not reported or assessed in this study. 	<ul style="list-style-type: none"> • Small study in a Belgian population with baseline low Se levels. • Selenium at a dose of 130 to 150 mcg/day IV restored Se levels to RR. • Results for parenteral versus oral routes were not reported separately.

Abbreviations: F = female; GSHPx = glutathione peroxidase; Hb = hemoglobin; HPN = home parenteral nutrition; IV = intravenous; LT = long-term; M = male; NPO = nothing by mouth; PN = parenteral nutrition; RBC = red blood cell; RR = reference range; Se = selenium; TPN = total parenteral nutrition; TE = trace elements

Source: Adapted from NDA 209379 Module 2.7.3 Table 34 and literature review.

15.9. Case Summaries of Selenium Deficiency in Adults

Table 20: Case Summaries of Selenium Deficiency in Adults

First Author, Year, Location	Case Age and Sex	Trace Element Information	Brief Narrative
Oguri et al. [202] 2012 Japan	40-year-old male with short-bowel syndrome on HPN for 3 years	<ul style="list-style-type: none"> Se (as sodium selenite) 100 mcg/day* administered IV for Se deficiency <p>*publication indicates 100 mg/day, but most likely should have been 100 mcg/day</p>	<p>Patient complained of visual loss, slurred speech and staggering gait and had macrocytosis; curly hair and whitened nail beds had developed 3 months before neurological symptoms. Serum Se was below the detection limit of 2.0 mcg/dL (normal RR). With selenium supplementation, hair and nail abnormalities gradually disappeared and MCV returned to normal over several months. Although deterioration of neurological symptoms stopped soon after initiation of Se replacement, the symptoms remained unchanged after 3 years of Se replacement.</p> <ul style="list-style-type: none"> The author does not include information in the publication on whether HPN included selenium prior to diagnosis of deficiency.
Ishida et al. [44] 2003 Japan	22-year-old female with short-bowel syndrome on HPN for 4 years	<ul style="list-style-type: none"> Se (as sodium selenite) 200 mcg/day IV for 2 weeks, then 100 mcg/day during hospitalization Se (as sodium selenite) 100 mcg/day orally on outpatient basis 	<p>During admission to hospital for intestinal obstruction, patient exhibited tiredness of lower limbs, whitened nail beds and macrocytosis. Plasma Se was below the assay detection limit (<2.5 mcg/dL, normal NR). Although clinical symptoms and parameters resolved after several weeks of selenium administration, plasma Se concentration remained below the measurable level. Selenium supplementation continued during hospitalization, but the Se level remained undetectable.</p> <ul style="list-style-type: none"> In 2003, this author states that selenium is often not routinely added to TPN formulations in Japan.
Yusuf et al. [203] 2002 United States	46-year-old male on TPN for 3 months	<ul style="list-style-type: none"> Se 150 mcg/day was added to TPN 	<p>Patient developed dilated cardiomyopathy but had little improvement following treatment with various cardiac medications. Further investigation showed the patient had an undetectable blood Se level; the TPN the patient had received for 3 months contained no Se. After Se supplementation over several weeks, marked improvement in clinical symptoms and echocardiographic findings was noted. When stabilized, the patient was taken off his heart failure medications and continued to receive TPN with added Se, with no recurrence of cardiomyopathy. Patient was also found to have peripheral neuropathy with bilateral foot drop during the same hospitalization that did not improve with Se supplementation. Repeat of Se level was not reported post Se supplementation.</p>

First Author, Year, Location	Case Age and Sex	Trace Element Information	Brief Narrative
Tsuda et al. [204] 1998 Japan	35-year-old male on home TPN for 13 years	<ul style="list-style-type: none"> • Se 100 mcg/day for 99 days • 200 mcg/day for 53 days <p>Route of selenium supplement was not reported.</p>	<p>Patient was hospitalized for evaluation of muscle weakness and increased serum creatine phosphokinase. Serum Se was very low (0.1 mcg/dL; normal 9.7 to 16 mcg/dL). After 3 months of Se supplementation, muscle weakness began to resolve, and serum creatine phosphokinase values began to decrease. However, the patient's muscle weakness did not disappear completely and the serum Se level was not normalized, so a higher dose of Se was administered, with normalization of creatine phosphokinase and serum Se level (9.6 mcg/dL) and resolution of muscle weakness.</p> <p>This case suggests that higher doses than 100 mcg/day may be needed to correct a deficiency state; however, it is possible that an adequate correction dose may be related to severity of deficiency.</p>
Levy et al. [34] 1994 United Kingdom	27-year-old male with a history of Crohn's disease receiving short-term (19 days) postoperative PN	<ul style="list-style-type: none"> • Se 32 mcg/day IV in PN • Se (as selenite) 100 mcg/day orally 	<p>Patient who had received post-operative PN supplemented with trace elements including 32 mcg/day selenium supplementation for 19 days presented with symptomatic tachycardia and chest pain, with markedly reduced serum Se levels (2.37 mcg/dL; normal 6.2 to 15.6 mcg/dL) and erythrocyte GSHPx activity (10 U/g Hgb, normal range 13 to 25 U/g Hgb. Patient was treated with an oral selenium supplement. After 3 months of supplementation with Se, electrocardiogram, serum Se, and red cell glutathione peroxidase activity had returned to normal.</p>
Kawakubo et al. [205] 1994 Japan	38-year-old male with short-bowel syndrome on long-term TPN	<ul style="list-style-type: none"> • Fresh frozen plasma containing Se initially administered • Se (as sodium selenite) 200 mcg/day IV 	<p>Patient experienced visual disturbances after 4 years of TPN and oral elemental diet, which included no selenium supplementation. Various neurological symptoms developed during the next 3 years that progressed to consciousness disturbance. He also had erythrocytic macrocytosis, low tri-iodothyronine, high thyroxine, extremely low blood Se value (3.6 mcg/dL; normal 12.2 to 35.8 mcg/dL). After selenium supplementation, macrocytosis, tri-iodothyronine and thyroxine values, and glutathione peroxidase activity normalized; however, the patient showed no improvement in progressive encephalopathy.</p>
Marcus [206] 1993 United States	49-year-old female receiving TPN following extensive removal of intraperitoneal metastases	<ul style="list-style-type: none"> • Se (as selenious acid) 200 mcg/day added to TPN 	<p>Patient developed muscle tenderness, limited painful shoulder, and stiffness in fingers, knees, and lower back within 3 months after initiation of selenium-free TPN. When examined 2 months later, the patient had a very stiff gait, difficulty maneuvering in the examination room, and a serum Se <5.0 mcg/dL; normal: 5.5 to 13 mcg/dL). Muscle tenderness improved with selenium supplementation and serum Se level increased to 10 mcg/dL. Inadvertent discontinuation of selenium was associated with a recurrence of extreme muscle tenderness; resumption of selenium replacement again resulted in a marked reduction of muscle tenderness.</p>

First Author, Year, Location	Case Age and Sex	Trace Element Information	Brief Narrative
Abrams et al. [207] 1992 United States	68-year-old male with short bowel syndrome on TPN	<ul style="list-style-type: none"> Se (as selenious acid) 40 mcg/day IV, initially, and increased to 80 mcg/day 	After 3 years of almost exclusive nourishment by TPN, the patient developed whitened nail beds. The patient's serum zinc values had been in the low-normal range (72 mcg/dL; normal 50 to 150 mcg/dL) and he had been receiving supplemental zinc (9 mg/day) for some time; serum zinc at time of nail bed changes was high-normal (145 mcg/dL). Trace element investigation for possible deficiency showed very low blood Se (<2 mcg/dL). The only clinical signs of selenium deficiency was whitened nail beds. After selenium supplementation, blood levels of Se rose (4 mcg/dL) and nail bed changes were reversed.
Reeves et al. [208] 1989 United States	22-year-old female with 6- to 8-week history of diarrhea, anorexia, malaise, and weight loss	<ul style="list-style-type: none"> Se 20 mcg/day as part of TPN for 5 days, increased to 200 mcg/day 	Patient was hospitalized with cardiac symptoms including profound generalized left ventricular hypokinesis, left ventricular ejection fraction of 10%, elevated pulmonary capillary wedge pressure, and reduced cardiac index; myocarditis was ruled out. Crohn's disease was diagnosed and TPN was initiated, including selenium supplementation of 20 mcg/day. Five days later, blood Se level was below normal (4 mcg/dL; normal 6 to 16 mcg/dL) and selenium supplementation increased to 200 mcg/day. Over the next several weeks of hospitalization, the patient's cardiovascular status improved and a repeat echocardiogram 4 weeks after the initial study showed near-total resolution of the previously documented left ventricular dysfunction and a left ventricular ejection fraction of 50%. A repeat Se level was not obtained.
Mansell et al. [209] 1987 United Kingdom	46-year-old male with intractable malabsorption on HPN	<ul style="list-style-type: none"> Zinc 13 mg/day for first 7 days and 6.5 mg/day thereafter After zinc restoration, Se (as sodium selenite) 79 mcg/day for 1 month; 31.6 mcg/day thereafter 	Patient complained of muscle weakness and discomfort (particularly in thighs) after approximately 15 months on home TPN, including zinc 20 µmol. Serum zinc was 45.8 mcg/dL (reference range 52.3 to 117.7 mcg/dL) and Se was <0.4 mcg/dL (reference range 6.32 to 15.8 mcg/dL). Serum zinc was first restored to normal levels without affecting muscle strength. Muscle strength increased with selenium supplementation. Muscle pain on exercise resolved.
Brown et al. [210] 1986 United States	33-year-old female with short bowel syndrome on home TPN	<ul style="list-style-type: none"> Se (as selenious acid) 400 mcg/day IV 	<p>During the first year of TPN, patient noted the onset of an inability to rise from a squatting position, rapid tiring when climbing stairs, and weakness when attempting to lift large or moderately heavy objects. After 4 years of TPN, her plasma, red cell, white cell, and platelet glutathione peroxidase activities and her plasma and red cell Se levels were extremely low. Within 6 weeks, IV selenium supplementation resulted in disappearance of symptoms, increase in proximal muscle strength, and return to normal in plasma and red cell Se levels and plasma and white cell glutathione peroxidase activities. Red cell glutathione oxidase activity returned to normal by 3 months.</p> <p>In the era prior to routine selenium supplementation in the United States, this case characteristically represents the essential nature of selenium as an additive to PN.</p>

First Author, Year, Location	Case Age and Sex	Trace Element Information	Brief Narrative
van Rij et al. [68] 1981 New Zealand	4 cases reported but only 2 cases received parenteral selenium supplementation: 3) 38-year-old female after 40 days of TPN for enterocutaneous fistula with muscle pain; plasma Se of 0.9 mcg/dL 4) 38-year-old male after 50 days of TPN for post-traumatic duodenal fistula and intra-abdominal sepsis; plasma Se of 0.8 mcg/dL	<ul style="list-style-type: none"> Reference range: 4.9 ± 0.1 mcg/dL Se administered as: <ul style="list-style-type: none"> 3) Selenomethionine 100 mcg/day IV for 15 days (dose was 115 mcg on 2 of these days) 4) Selenomethionine 250 mcg for 2 days and 100 mcg/day for 7 days IV, followed by 100 mcg/day orally for 18 days 	<p>Patient #3 had muscle pain that was responsive to selenium supplementation. Symptoms improved by Day 5 of supplementation. Plasma and urinary Se increased but remained below the lower normal range; neither erythrocyte Se levels nor glutathione peroxidase activity were increased. No symptoms of Se toxicity were reported.</p> <p>Patient #4 had increasing urinary excretion of Se with IV supplementation for 9 days; TPN was discontinued and the patient received oral Se. Plasma and erythrocyte Se increased; after a transient fall with the change to oral supplement, urinary Se continued to increase and eventually exceeded the normal level. It was unclear whether symptoms of selenium deficiency were assessed for this patient. Symptoms of selenium deficiency/toxicity were not reported.</p>

* Denotes literature identified by DEPI review

Abbreviations: Hgb = hemoglobin; HPN = home parenteral nutrition; IV = intravenous; MCV = mean corpuscular volume; NR = not reported; PN = parenteral nutrition; Se = selenium; TPN = total parenteral nutrition

Source: Adapted from NDA 209379 Module 2.7.3 Table 34 and literature review.

15.10. Summary of Observational Studies Evaluating Parenteral Selenium in Neonatal and Pediatric Patients

Table 21: Summary of Observational Studies Evaluating Parenteral Selenium in Neonatal and Pediatric Patients

First Author, Year, Location	Study Objective	Patient Population Number of Patients Females/Males Age	Trace Element Administration, Duration	Reported Findings	Reviewer Comments
Etani et al. [189] 2014 Japan	To investigate the clinical features of selenium deficiency in children and adolescents receiving PN without selenium and EN with either reduced or no selenium.	Children and adults with intestinal dysfunction and/or neurological disabilities receiving PN: <ul style="list-style-type: none"> N=5 (95 patients reviewed but investigators only reported interventional results on patients with serum Se <2 mcg/dL) but summarized the remaining subjects: Twenty-three patients were nourished through nutritional products containing reduced doses of selenium. In addition to PN and/or elemental diet (ED), trace element supplements containing selenium were consumed by 13 patients. Most patients received 1 pack of V-ACCEL® (NUTRI Inc., Mie, Japan) every day, which contained 50 mcg of selenium and 5 mg of zinc. 2F/1M Age range: 2 to 20 years 	Patients with selenium levels <2 mcg/dL (5 patients) received supplementation with trace elements including selenium 150 mcg to 350 mcg/week (4 patients) and rice water/fish soup twice daily (1 patient) Duration of supplementation was 12 months	<ul style="list-style-type: none"> All 5 patients with Se levels <2 mcg/dL presented with various clinical manifestations including hair browning (5 patients), macrocythemia (4 patients), nail whitening (3 patients), and cardiac dysfunction (1 patient). Mean serum Se levels increased to 6.6 mcg/dL (range: 3.9 to 10.2 mcg/dL) with Se supplementation. After 12 months of Se supplementation, the clinical features of selenium deficiency improved in all 5 patients. 	<ul style="list-style-type: none"> The underlying diseases in the patients receiving TPN were notable intestinal dysfunction and neurological disorders preventing oral intake; comorbidities could be exacerbated by selenium deficiency and is often irreversible in other case summaries reviewed. Amount of selenium in fish soup could not be quantified therefore the amount of selenium supplementation could not be determined in 1 patient. Various clinical manifestations of selenium deficiency were observed at serum Se levels <2 mcg/dL suggesting that 2 mcg/dL could be a cutoff level below which symptoms of deficiency are likely to develop.

First Author, Year, Location	Study Objective	Patient Population Number of Patients Females/Males Age	Trace Element Administration, Duration	Reported Findings	Reviewer Comments
Davis et al. [166] 2014 United States	To investigate the impact of the selenium shortage on the selenium status of patients with severe intestinal failure	Children with intestinal failure on TPN who were >1 year of age at the onset of the parenteral Se shortage: <ul style="list-style-type: none">• N=5• 1F/4M• Age range: 2 to 13 years	TPN supplemented with selenium 50 to 200 mcg/day, zinc, copper, and manganese Duration of Se shortage at the institution lasted 9 months due to a national shortage. Approximately 6 months following depletion of the institution's Se supply, Se supplementation using MTE-5 was identified as a source of parenteral Se	<ul style="list-style-type: none">• All 5 patients had normal serum Se concentrations (normal range 7 to 15 mcg/dL) prior to the Se shortage and levels fell to below normal between 3 and 6 months into Se shortage period (all <2.0 mcg/dL).• No symptoms associated with Se deficiency were observed.• Serum Se levels recovered after Se supplementation was reinstated.	<ul style="list-style-type: none">• Weight was not reported so the actual weight-based dose may have varied between patients and the exact dose is unknown.• When serum Se level started to rise again after Se supplementation resumed with MTE-5, pediatric patients received a reduced dose of Se between 10 and 26 mcg/day.
Masumoto et al. [43] 2007 Japan	To report on finding of 6 Se-deficient infants who received LT NS (PN and/or ED) without Se supplementation	Infants receiving long-term NS diagnosed with Se deficiency (growth retardation, alopecia with pseudoalbinism): <ul style="list-style-type: none">• N=6• 3F/3M• Mean age of onset of Se deficiency: 6.3±4.0 months• Mean duration of NS without Se: 5.2±4.5 months	2 patients received IV Selenium supplementation 5 mcg/kg/day IV; 1 patient received enteral Se 5 mcg/kg/day for 1 month and then 3 mcg/kg/day; 3 patients had enteral Se between 3 and 7.5 mcg/kg/day	<ul style="list-style-type: none">• At time of diagnosis, all patients had low serum Se level (4 patients <2.0 mcg/dL; 2 patients were 3.2 and 3.3 mcg/dL).• Serum Se concentrations increased to within the normal range (5 to 15 mcg/dL) in all patients with IV and enteral supplementation at 3 months after start of Se supplementation.• All patients had growth retardation, alopecia with pseudoalbinism, which improved after Se supplementation.	<ul style="list-style-type: none">• 4 out of 6 patients had serum Se levels <2 mcg/dL at diagnosis.• Low serum Se levels in infants may present as growth retardation and alopecia with pseudoalbinism.• Other causes of growth retardation alopecia were investigated and there were no other TE deficiencies.

First Author, Year, Location	Study Objective	Patient Population Number of Patients Females/Males Age	Trace Element Administration, Duration	Reported Findings	Reviewer Comments
Klinger et al.* [211] 1999 Israel	To evaluate whether Se supplementation with 2 mcg/kg/day by PN maintains Se plasma levels in ELBW neonates and whether hypothyroidism is related to Se deficiency in this population	Preterm ELBW (<1000 g) who received more than two-thirds of their calories parenterally: • N=29 • Sex not reported • Mean GA: 26±1.6 weeks	PN + Se: 2 mcg/kg/day Se levels measured at Day 10 (7 days after start of selenium supplementation)	<ul style="list-style-type: none"> 2 pre-term neonates died (cause not reported). Mean plasma Se was 4.3 mcg/dL on Day 10 of life (reference range: ≥5.7 mcg/dL). No significant correlation was found between plasma Se and TSH. 	<ul style="list-style-type: none"> Plasma Se remained low despite supplementation of 2 mcg/kg/day. Baseline and subsequent Se levels were not reported. Therefore, it is difficult to draw conclusions about the effect of parenteral selenium supplementation in pre-term neonates based on this study. The authors conclude that prematurity and low birth weight can contribute to low blood selenium in premature infants. Selenium supplementation seems to minimize or prevent clinical complications caused by prematurity. Due to the high risk of complications in ELBW neonates, the significance of 2 deaths is unclear but suggests that this is a higher risk population with increased selenium requirements and susceptibility to selenium deficiency.

First Author, Year, Location	Study Objective	Patient Population Number of Patients Females/Males Age	Trace Element Administration, Duration	Reported Findings	Reviewer Comments
Vinton et al. [88] 1987 U.S.	Report on newly recognized clinical manifestations of selenium deficiency (erythrocyte macrocytosis and pseudoalbinism) and the need for selenium supplementation in patients who receive long-term TPN	Selenium deficient children dependent on TPN for 90% or more of their nutritional needs: <ul style="list-style-type: none">• N=4• Sex not reported• Age at start of TPN: 0.2 to 3 months	Selenium supplementation with 2 mcg/kg/day	<ul style="list-style-type: none">• Initial serum Se levels in serum and hair were 3.8 ± 1.1 mcg/dL (normal range: 8.5 to 12.5 mcg/dL) and 0.34 ± 0.13 mcg/g (normal range not reported), respectively.• Clinical manifestations included:<ul style="list-style-type: none">◦ Erythrocyte macrocytosis (3 patients)◦ Loss of pigmentation in hair and skin (2 patients)◦ Elevated transaminase and CK (2 patients)◦ Muscle weakness (1 patient)• After 6 months of selenium supplementation, mean serum Se levels rose to 8.1 ± 2.2 mcg/dL, MCV and CK also normalized and muscle weakness improved in affected patients.• After 6 to 12 months of selenium supplementation, hair Se content had increased threefold. Patients with decreased pigmentation became darker skinned and hair color changed from blond to dark brown.	<ul style="list-style-type: none">• Low serum Se levels may be associated with, loss of pigmentation, elevated CK and transaminases, and muscle weakness.• The authors states that PN selenium supplementation not routine at the time of this publication.

* Denotes literature identified by DEPI review

Abbreviations: BF = breast fed; ED = elemental diet; ELBW = extremely low birth weight; F = female; FF = formula fed; GA = gestational age; GI = gastrointestinal; GSHPx = glutathione peroxidase; Hgb = hemoglobin; IV = intravenous; KPN = Ketogenic parenteral nutrition; LT = long-term; M = male; MCV = mean corpuscular volume; NS = nutritional support; PN = parenteral nutrition; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TE = trace elements; TPN = total parenteral nutrition; ULN = upper limits of normal; VLBW = very low birth weight; WBC = white blood cell

Source: Reviewer Generated Based on NDA 209379 Submission Module 2.9.3 and Additional Literature

15.11. Case Summaries of Selenium Deficiency in Pediatric Patients

Table 22: Case Summaries of Selenium Deficiency in Pediatric Patients

First Author, Year,	Patient Population Number of Patients Females/Males Age	Trace Element Administration, Duration	Reported Findings	Reviewer Comments
Terada et al. [212]	10-year-old male (weight=25kg) with short-bowel syndrome on long-term TPN for >9 years.	Selenium 4 mcg/kg/day administered IV for approximately 5 months, after temporary interruption, dose increased to 8 mcg/kg/day for 6 months, then gradually decreased to 7.2 mcg/kg/day for 1 month, and 4.8 mcg/day for approximately 6.5 months.	<ul style="list-style-type: none">Baseline plasma and erythrocyte Se concentrations were low at 8.5 mcg/dL (reference range: 91 to 159 mcg/dL) and 9.9 mcg/dL (reference range: 22.7 to 37.4 mcg/dL), respectively.Patient complained of bilateral quadricep pain prior to supplementation.One month after start of Se supplementation, symptoms disappeared and the plasma Se level was within the normal range, but erythrocyte Se concentrations remained low.When administration was suspended 5 months later due to catheter-induced fever, plasma and erythrocyte Se concentrations decreased and the symptoms recurred.Restart of Se at 8 mcg/kg/day increased plasma and erythrocyte Se levels to within normal range.GSHPx activity values were within the normal range before administration of Se and did not change significantly with Se supplementation.When Se dose was decreased to 4.8 mcg/kg/day, the plasma and erythrocyte Se levels remained normal and did not change significantly; no recurrence of symptoms was observed.	<ul style="list-style-type: none">Reference range was established using 16 children aged 6 to 15 years old.

First Author, Year, Case report	Patient Population Number of Patients Females/Males Age	Trace Element Administration, Duration	Reported Findings	Reviewer Comments
Kelly et al. [213] 1988 Case report	21-month-old female with microvillous atrophy on long-term HPN for 17 months.	Selenium 1.5 mcg/kg/day was added to PN (zinc, manganese, and other trace elements already present)	<ul style="list-style-type: none"> Child presented with regression of walking skills, abnormal electromyograph, and myopathy on muscle biopsy after receiving PN for 17 months. Plasma Se: <0.4 mcg/dL (reference range: 6.3 to 12.6 mcg/dL), erythrocyte GSHPx was undetectable (reference range: 13 to 25 U/L Hgb), and plasma GSHPx: 6 U/L (reference range: 90 to 350 U/L). Following replacement with IV selenium, muscle pain and tenderness resolved within 3 days and walking skills regained within 6 weeks. EMG at 6 months was normal. After 3 months of selenium replacement, plasma Se: 4.2 mcg/dL; erythrocyte GSHPx was within normal limits. 	<ul style="list-style-type: none"> All Se assays were well below the reference range but did not appear to correlate with the degree of symptomatology that had been reported with Se deficiency. The author concludes "the Reference Daily Intake of selenium for children aged 1 to 3 years has been suggested to be 20 to 80 mcg/day but the actual requirement is unknown."

First Author, Year, Case report	Patient Population Number of Patients Females/Males Age	Trace Element Administration, Duration	Reported Findings	Reviewer Comments
Kien & Ganther [214] 1983	6-year-old male with chronic secretory diarrhea and intolerance to food on TPN for 1.5 years.	<p>Initial TPN with selenium 42 mcg/day, zinc 2.1 to 2.6 mg/day, copper 0.3 to 0.5 mg/day, manganese 0.075 mg/day</p> <p>At Month 33 on TPN, Se supplementation was initiated, initially at 400 mcg/day with eventual decrease to 96.6 mcg/day (\approx3 mcg/kg/day) at 39 months</p>	<ul style="list-style-type: none"> Child developed intermittent leg muscle pain and tenderness as well as elevation in SGOT (AST), SGPT (ALT) and CK after receiving TPN for 1.5 years. Six months later, the patient developed white nail beds. Retrospective analysis of serum and urine samples showed very low serum Se concentrations: 0.31 to 0.72 mcg/dL and urine excretion (0.0 to 8.9 mcg/day). Serum Se levels increased with Se supplementation. Liver biochemistries and CK improved; fingernail bed abnormalities and myalgia resolved after therapy. 	<ul style="list-style-type: none"> Patients can have very low Se levels without becoming notably symptomatic. The author states "however, it is unclear from these reports whether subclinical evidence for hepatocellular or muscle cell damage was sought.... Our results suggest that serum enzyme activities and fingernail bed abnormalities could be early signs of human selenium deficiency. These results indicate that severe selenium deficiency, with Se levels as low as any reported previously, can exist for more than 2 years without overt severe clinical manifestations."

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BF = breast fed; F = female; GSHPx = glutathione peroxidase; CK = creatine kinase; FF = formula fed; GA = gestational age; Hgb = hemoglobin; IV = intravenous; M = male; MCV = mean corpuscular volume; PN = parenteral nutrition; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TE = trace elements; TPN = total parenteral nutrition; ULN = upper limits of normal; WBC = white blood cell

Source: Reviewer Generated Based on NDA 209379 Submission Module 2.9.3

15.12. Summary of Literature Reported Death Associated With Acute Oral Selenium Toxicities

Table 23: Summary of Literature Reported Death Associated With Acute Oral Selenium Toxicities

Author, Year	Patient Description*	Oral Se Dose	Se Levels	Reported Signs and Symptoms	Comments
Spiller & Pfiefer [215] 2007	36-year-old female	Unknow amount ingested	Not reported	<ul style="list-style-type: none"> • Nausea, vomiting, diarrhea • Abdominal pain • Weakness chest pain • Dyspnea • Pulmonary edema • Syncope • ECG: initial tachycardia, prolonged QT, AV nodal block; progressed to bradycardia, ST wave changes; eventual VF and asystole arrest 	<ul style="list-style-type: none"> • Patient was unsuccessfully resuscitated and died 15-17 hours after initial onset of symptoms. • No myocardial necrosis on autopsy. • High levels of Se in postmortem tissue examination.
	36-year-old male with hypertension	Unknow amount ingested	Whole blood Se: 190 mcg/dL (RR: 8-13 mcg/dL)	<ul style="list-style-type: none"> • Chest pain • Abdominal pain • Nausea, vomiting, diarrhea • Hypotension • Nystagmus • Respiratory failure • ECG: Tachycardia, 1st degree AV block, ST depression in anterior and lateral leads • Labs: AKI, lactic acidosis • Cardiomyopathy with EF 15% (baseline 59%) 	<ul style="list-style-type: none"> • Patient was unsuccessfully resuscitated and died 16 to 18 hours post ingestion. • Concomitant medication: metoprolol, doxepin, and escitalopram
See et al. [12] 2006	75-year-old male (PMHx not reported)	10 g	Serum Se: 537.2 mcg/dL (RR: 4.7 to 18.2 mcg/dL)	<ul style="list-style-type: none"> • Vomiting, diarrhea • Abdominal pain • Hypotension • ECG: prolonged QT, VT • Lab: acidosis, hypokalemia 	<ul style="list-style-type: none"> • Patient was unsuccessfully resuscitated and died 16 hours post ingestion.
Hunsaker et al. [9] 2005	24-year-old male with depression and alcohol abuse	Unknown amount ingested: G96 gun-blue 59.1 ml bottle which contain 1 to 5% of selenious acid	Serum Se: 3,000 mcg/dL (1 hr post-ingestion) (RR: 6.6 to 10.4 mcg/dL)	<ul style="list-style-type: none"> • Agitation • Vomiting • Garlic odor • ECG: sinus tachycardia with non-specific ST wave changes and QT prolongations; progressed to VF arrest • Labs: leukocytosis, elevated INR 	<ul style="list-style-type: none"> • Patient was unsuccessfully resuscitated and died 4 hours post-ingestion.

Author, Year	Patient Description*	Oral Se Dose	Se Levels	Reported Signs and Symptoms	Comments
Quadrani et al. [216] 2000	22-month-old male (15 kg)	15 ml of gun blue solution containing 9.3% selenious acid, 4.6% nitric acid, 4.6% copper nitrite	Blood Se: 1200 mcg/dL	<ul style="list-style-type: none"> • Hypoxia • Altered mental status • Cyanosis • Pulmonary edema • VF • Lab: acidosis 	<ul style="list-style-type: none"> • Patient was unsuccessfully resuscitated and died 3 hours post-ingestion.
Koppel et al. [217] 1986	17-year-old male	10 g	Blood Se: 3800 mcg/dL (RR: 18 mcg/dL)	<ul style="list-style-type: none"> • Coma • Asystole • Apnea 	<ul style="list-style-type: none"> • Patient was unsuccessfully resuscitated and died.
Matoba et al. [218] 1986	40-year-old female	Unknown quantity of gun blue agent	Blood Se: 260 mcg/dL (RR: 9±3 mcg/dL)	<ul style="list-style-type: none"> • Vomiting, diarrhea • Altered mental status • Chest and abdominal pain • Tachycardia • Hypotension 	<ul style="list-style-type: none"> • Cardiac arrest with unsuccessful resuscitation 8 hours post-ingestion.
Nantel et al. [219] 1985	2-year-old	15 ml of gun blue solution containing selenious acid		<ul style="list-style-type: none"> • Vomiting • Garlic odor • Second degree burns of esophagus and stomach • Respiratory failure • Cardiac arrhythmia • Coma • Labs: leukocytosis, elevated CK, metabolic acidosis 	<ul style="list-style-type: none"> • Hospital course complicated by secondary Legionella infection with eventual death at 17 days after ingestion.
Pentel et al. [220] 1985	52-year-old female (PMHx not reported)	gun blue	243.5 mcg/dL	<ul style="list-style-type: none"> • Garlicky odor • Hypotension • Respiratory failure • Myopathy 	<ul style="list-style-type: none"> • Death at 8 days post ingestion

*Patients were previously healthy unless otherwise stated.

Abbreviations: AKI = acute kidney injury; AV = atrioventricular; CK = Creatine kinase; ECG = electrocardiogram; EF = ejection fraction; GI = gastrointestinal; GSHPx = glutathione peroxidase; hr = hour; IM = intramuscular; LT = long-term; PMHx = past medical history; RR = reference range; Se = Selenium; TB = total bilirubin; TPN = total parenteral nutrition; TWI = T-wave inversion; VF = ventricular fibrillation

Source: Reviewer Generated Based on Submitted Literature

15.13. Summary of Literature Reporting Non-Fatal Acute Oral Selenium Toxicities

Table 24: Summary of Literature Reporting Non-Fatal Acute Oral Selenium Toxicities

Author, Year	Patient Description	Oral Se Dose	Se Levels	Observed Signs and Symptoms	Comments
Gasmi et al. [10] 1997	29-year-old male	"Mouthful" (30 g/L)	Peak plasma Se: 93.1 mcg/dL (3 hrs post ingestion)	<ul style="list-style-type: none"> Asymptomatic Transient elevation in CK on Day 3 to 6 post ingestion (values not reported) 	
	56-year-old male	1.7 g	Peak plasma Se: 271.6 mcg/dL (3 hours post ingestion)	<ul style="list-style-type: none"> Abdominal pain Nausea, vomiting, diarrhea ECG changes: TWI in leads III and AVF Hypoxemia Labs: transient elevated CK on Day 1; hyperbilirubinemia Day 2 to 5 	<ul style="list-style-type: none"> Plasma Se levels rise as early as 3 hours post ingestion and showed subsequent decline.
Lombeck et al. [221] 1987	2-year-old female	Unknown quantity (up to 2.9 g possible) of gun clue agent	Plasma Se: 158 mcg/dL (5 hours post ingestion)	<ul style="list-style-type: none"> Vomiting, diarrhea Muscle spasms Labs: leukocytosis 	<ul style="list-style-type: none"> Recovered within 24 hours.
Sioris et al. [222] 1980	5 adults	1 to 5 mg/kg	Serum Se: 41 to 89 mcg/dL	<ul style="list-style-type: none"> Nausea, vomiting, diarrhea Abdominal pain Tremor 	<ul style="list-style-type: none"> Recovered within 24 hours.
Civil et al. [188] 1978	15-year-old female from farming district Weight=52.5 kg	≈1.16 g 400 ml of sheep drench (sodium selenate 2.9 mg/ml)	Initial serum Se: 310 mcg/dL (RR: 6 to 11.1 mcg/dL)	<ul style="list-style-type: none"> Initial vomiting and loose stools Myalgia Irritability ECG changes: diffuse T-wave flattening initially progressed to TWI in anterior and lateral leads along with prolonged QT interval Labs: elevated TB 	<ul style="list-style-type: none"> Treated with gastric lavage and vitamin C 1g IM Day 1 and then 4d daily PO. Recovered fully and discharged after 17 days of hospitalization.

Abbreviations: AKI = acute kidney injury; CK = Creatine kinase; ECG = electrocardiogram; EF = ejection fraction; GI = gastrointestinal; GSHPx = glutathione peroxidase; hrs = hours; IM = intramuscular; LT = long-term; RR = reference range; Se = Selenium; TB = total bilirubin; TPN = total parenteral nutrition; TWI = T-wave inversion; VF = ventricular fibrillation

Source: Reviewer Generated Based on Review of Submitted Literature

15.14. Summary of Literature for Chronic Oral Selenium Toxicities

Table 25: Summary of Literature for Chronic Oral Selenium Toxicities

Author, Year	Population	N	Oral Se Dose (per day)	Duration of Exposure	Se Levels (mcg/dL)	Observed Signs and Symptoms	Comments
MacFarquhar et al. [193] 2010	Healthy adults taking dietary supplement	201	3.4 to 244.8 mg	1 to 109 days	Serum Se ranged from 32.1 to 150 mcg/dL ^e	<ul style="list-style-type: none"> • Diarrhea (78%) • Fatigue (72%) • Hair loss (70%) • Joint pain (67%) • Nail discoloration or brittleness (61%) • Nausea (57%) • Headache (45%) • Tingling (39%) • Vomiting (52%) • Fever (21%) • Ataxia (13%) 	<ul style="list-style-type: none"> • Most symptoms persisted even after cessation of ingestion for ≥90 days. • Additional symptoms included memory loss, mood changes, muscle pains/aches and weakness.
Reid et al. [223] 2004	Men with biopsy-proven prostate cancer	8	1.6 mg	Up to 24 mo	Mean plasma Se: 49.2 mcg/dL	<ul style="list-style-type: none"> • Brittle nails • Stomach upset • Dizziness 	<ul style="list-style-type: none"> • Manifestations of toxicity did not correlate with peak plasma Se levels.
		16	3.2 mg	Up to 24 mo	Mean plasma Se: 64 mcg/dL	<ul style="list-style-type: none"> • Brittle nails and hair • Stomach upset • Dizziness • Garlic breath 	
Clark et al. [224] 1996	36-year-old male taking vitamin supplement	1	Up to 8 mg	2 weeks	Serum Se: 65.4 mcg/dL (RR 5.5 to 13 mcg/dL)	<ul style="list-style-type: none"> • Diarrhea • Alopecia • Paresthesia • Nail changes 	<ul style="list-style-type: none"> • Symptoms resolved after discontinuing supplement. • Laboratory analysis by the FDA demonstrated between 500 and 1000 times the labeled amount of selenium per tablet (0.8 mcg/tab).

^e Individual Se levels not reported and correlation with symptoms was not reported.

Author, Year	Population	N	Oral Se Dose (per day)	Duration of Exposure	Se Levels (mcg/dL)	Observed Signs and Symptoms	Comments
MMWR [191] 1984	Healthy adult taking dietary supplement	1	27.3 mg	10 weeks	Serum Se: 52.8 mcg/dL	<ul style="list-style-type: none"> • Alopecia • White streaking on nail • Paronychia • Nausea and vomiting 	<ul style="list-style-type: none"> • Onset of nail findings and hair loss at 11 days. • Analysis of the selenium tablets from one lot revealed a selenium level of 27.3 mg per tablet (182 times higher than labeled).
Yang et al. [190] 1989	5 cases with long-persisting clinical signs of selenosis 349 adult inhabitants of seleniferous region in Hubei, China	5		Chronic	Blood Se: 105.4 to 185.4 mcg/dL	<ul style="list-style-type: none"> • Nail and hair loss • Laboratory: increased prothrombin time when blood Se >100 mcg/dL; increases in WBC 	<ul style="list-style-type: none"> • Symptoms of selenosis were found at Se intake of \geq910 mcg/day with a corresponding blood Se level of 101 to 228.
Yang et al. [7] 1983	Inhabitant of seleniferous region in Hubei, China	248	3.2 to 6.69 mg	Chronic	Blood Se: 130 to 750 mcg/dL	<ul style="list-style-type: none"> • Loss of hair and loss of pigment in hair • Brittle nails • Pruritic Rash on scalp and other skin lesions • Nervous system symptoms including peripheral paresthesia, hyperreflexia, convulsions and 1 case of hemiplegia in a 40-year-old female • Myalgia in extremities 	<ul style="list-style-type: none"> • Symptoms resolved when diet was changed. • Subjects with neurological effects required longer time for symptom resolution (duration of symptoms not reported).

Abbreviations: GI = gastrointestinal; GSHPx = glutathione peroxidase; IM = intramuscular; LT = long-term; Se = Selenium; RR = reference range

Source: Reviewer generated based on literature review

15.15. Signatures

APPEARS THIS WAY ON ORIGINAL

Appendices 15.15 - Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGE D/ APPROVED
Toxicologist	Jackye Peretz	OND/ODEIII/DGIEP	Sections: 5 Reviewed/Edited: 5 Appendices: None	Select up to two: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Cleared
Supervisory Pharmacologist	Sushanta Chakder	OND/ODEIII/DGIEP	Sections: 5 Reviewed/Edited: 5 Appendices: None	Select up to two: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Cleared

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ACKNOWLEDGED/APPROVED	AUTHORED/ACKNOWLEDGED/APPROVED
Clinical Pharmacology Reviewer	Jie (Jenny) Cheng	OTS/OCP/DCPIII	<p>Section authored: 6</p> <p>Reviewed/Edited/Cleared: 6</p>	<p>Select up to two:</p> <p><input checked="" type="checkbox"/> Authored</p> <p><input type="checkbox"/> Cleared</p>
Clinical Pharmacology Team Leader	Insook Kim	OTS/OCP/DCPIII	<p>Sections:</p> <p>Reviewed/Edited/Cleared: 6</p>	<p>Select up to two:</p> <p><input type="checkbox"/> Authored</p> <p><input checked="" type="checkbox"/> Cleared</p>

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Regulatory Affairs/ Project Management	Thao Vu	OND/ODEIII/DGIEP	Sections: All	Select up to two: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Acknowledged <input type="checkbox"/> Cleared
	Signature: Thao M. Vu -S			<small>Digitally signed by Thao M. Vu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Thao M. Vu -S, 0.9.2342.19200300.100.1.1=2001699412 Date: 2019.04.29 11:53:54 -04'00'</small>
Deputy Director (Acting) Signatory	Bindi Nikhar	CDER/OND/ODEIII	Section Authored: 14 Cleared: All	Select up to two: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Cleared
	Signature: Bindi M. Nikhar -S			<small>Digitally signed by Bindi M. Nikhar -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300198015, cn=Bindi M. Nikhar -S Date: 2019.04.29 11:39:01 -04'00'</small>
Clinical Team Leader	Stephanie O. Omokaro	OND/ODEIII/DGIEP	Section Authored: 1.3 Reviewed/Edited/Cleared: ALL	Select up to two: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Cleared
	Signature: Stephanie Omokaro -S			<small>Digitally signed by Stephanie Omokaro -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0012226969, cn=Stephanie Omokaro -S Date: 2019.04.26 08:49:33 -04'00'</small>
Clinical Reviewer	Yang- Veronica Pei	OND/ODEIII/DGIEP	Sections Authored: 1.1,1.2,1.4,2,3,7,8,9,11,12,13,17 Reviewed/Edited/Cleared: 1.3	Select up to two: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Cleared
	Yang Veronica Pei -S			<small>Digitally signed by Yang Veronica Pei -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001971532, cn=Yang Veronica Pei -S Date: 2019.04.26 08:29:16 -04'00'</small>

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DPMH Reviewer	Erica Radden	OND/ODEIV/DPMH	Sections Authored: 10 Reviewed/Edited/Cleared: 10	Select up to two: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Cleared
	Signature:  Erica Radden -A5 <small>Digitally signed by Erica Radden A5 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Erica.Radden.A5, o=9.2342.19200300.100.11=2000948362 Date: 2019.04.26 16:34:19.04'00'</small>			
DPMH Team Leader	Mona Khurana	OND/ODEIV/DPMH	Sections Authored: Reviewed/Edited/Cleared:10	Select up to two: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Cleared
	Signature: Mona Khurana <small>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=PIV, serialNumber=D72A10D821086CD9D61915A16859010872 447328872A8243EE Date: 2019.04.28 21:58:44 -04'00'</small>			
DPMH Deputy Director	John J. Alexander	OND/ODEIV/DPMH	Sections Authored: Reviewed/Edited/Cleared:10	Select up to two: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Cleared
	Signature: John J. Alexander -S <small>Digitally signed by John J. Alexander -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, o=9.2342.19200300.100.1.1=1300100694, cn=John J. Alexander -S Date: 2019.04.30 10:32:37 -04'00'</small>			

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DEPI-I Reviewer	Joel Weissfeld	OSE/OPE/DEPI-I	Section 9.2. Evaluation of Systematic Review of Medical Literature	Select up to two: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Cleared
				Signature: Joel L. Weissfeld -S <small>Digitally signed by Joel L. Weissfeld -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001545844, cn=Joel L. Weissfeld -S Date: 2019.04.29 09:31:58 -04'00'</small>
DEPI-I Team Leader	Patricia Bright	OSE/OPE/DEPI-I	Section 9.2. Evaluation of Systematic Review of Medical Literature	Select up to two: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Cleared
				Signature: Patricia L. Bright -S <small>Digitally signed by Patricia L. Bright -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000563850, cn=Patricia L. Bright -S Date: 2019.04.29 09:49:18 -04'00'</small>
DEPI-I Deputy Director	Sukhminder Sandhu	OSE/OPE/DEPI-I	Section 9.2. Evaluation of Systematic Review of Medical Literature	Select up to two: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Cleared
				Signature: Sukhminder K. Sandhu -S <small>Digitally signed by Sukhminder K Sandhu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300396896, cn=Sukhminder K Sandhu -S Date: 2019.04.29 10:10:45 -04'00'</small>

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DPV Reviewer	Jamie Klucken	OSE/OPE/DPV-I	8.2.4 Safety Concerns Identified Through Post-Market Experience	Select up to two: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Cleared
	Signature: Jamie L. Klucken -S			Digitally signed by Jamie L. Klucken -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002553241, cn=Jamie L. Klucken -S Date: 2019.04.26 07:27:46 -04'00'
DPV Team Leader	Lisa Harinstein		Sections Authored: Reviewed/Edited/Cleared: 8.2.4 Safety Concerns Identified Through Post-Market Experience	Select up to two: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Cleared
	Signature: Lisa M. Harinstein -S			Digitally signed by Lisa M. Harinstein -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001906839, cn=Lisa M. Harinstein -S Date: 2019.04.26 07:29:55 -04'00'
DPV Deputy Director	Monica Munoz		Sections Authored: Reviewed/Edited/Cleared: 8.2.4 Safety Concerns Identified Through Post-Market Experience	Select up to two: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Cleared
	Signature: Monica Munoz -S			Digitally signed by Monica Munoz -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Monica Munoz -S, 0.9.2342.19200300.100.1.1=2000546825 Date: 2019.04.26 07:33:09 -04'00'

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THAO M VU
04/30/2019 05:52:55 PM

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