CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209376Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 8, 2020

To: Thao Vu, Regulatory Project Manager, (DGIEP)

Joette Meyer, Associate Director for Labeling, (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for Tralement (trace elements injection 4*), for intravenous use

NDA: 209376

In response to DGIEP's consult request dated September 12, 21019, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA submission for Tralement..

PI: OPDP has no comments on the proposed labeling based on the draft PI received by electronic mail from DGIEP on June 1, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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MEETA N PATEL
06/09/2020 10:20:54 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 30, 2020
Requesting Office or Division:	Division of Hepatology and Nutrition (DHN)
Application Type and Number:	NDA 209376
Product Name and Strength:	Tralement (trace elements injection 4*) injection, *Each mL provides: zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg
Applicant/Sponsor Name:	American Regent
OSE RCM #:	2019-1889-1
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader (Acting):	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on April 24, 2020 for Tralement. Division of Hepatology and Nutrition (DHN) requested that we review the revised container label and carton labeling for Tralement (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Vee S. Label and Labeling Review for Tralement (NDA 209376). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 18. RCM No.: 2019-1889.

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SARAH K VEE
04/30/2020 10:27:45 AM

ASHLEIGH V LOWERY
04/30/2020 02:49:43 PM

Memorandum (Neonatal-Perinatal Medicine Consultation)

To: Yao-Yao Zhu, MD; Medical Officer / Clinical Reviewer
Thao Vu, RPh; Regulatory Project Manager
DHN/OII/OND/CDER

From: Gerri R. Baer, MD
Lead Medical Officer, OPT/OCPP/OC

Through: Susan McCune, MD
Director, OPT/OCPP/OC

Date: April 24, 2020

Subject: Neonatal-Perinatal Medicine Consultation for NDA 209376 Tralement™; assessment for neonates and young infants

MATERIALS REVIEWED:

1. Clinical Information Amendment, American Regent; 6 December 2019
2. Proposed Prescribing Information / Product Label for Tralement™; received April 13, 2020
3. Medical Policy Council Background Document to discuss NDAs 209379 (Selenious acid), 209377 (Zinc sulfate), and 209376 (Multitrace Elements); February 22, 2019; DGIEP

Published Literature
The reference list is included at the end of the consultation, following the recommendations.

NEONATAL-PERINATAL MEDICINE CONSULTATION QUESTION(S):

Multitrace Element (MTE) is currently available as an unapproved but marketed product. The application was granted Fast Track and Rolling Review on April 17, 2017 and is currently in Rolling Review with the last piece for CMC, 9 months stability data received on 9/5/2019.

The proposed indication is a source of zinc, copper, selenium, and manganese for parental nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. The Applicant is relying on published literature for their 505(b)2 application. The Applicant has provided separate efficacy and safety summaries for the pediatric population. While the Applicant has indicated that the current formulation is proposed for those ≥10 kg and they intend to develop a neonatal formulation, we request OPT's assistance in review (b) (4)

BACKGROUND:

Neonates and young infants with a broad range of medical and surgical conditions require parenteral nutrition (PN), during times when provision of enteral nutrition is impossible or inadequate to completely meet all nutritional requirements. In addition to providing the macronutrients, minerals, and vitamins that are needed for growth and metabolism, PN must also provide essential trace elements at the correct doses to avoid either deficiency or toxicity.

Trace element (TE) products administered as additives to PN have been largely in the marketed unapproved category. Dosing recommendations have been based on expert consensus from groups such as the Institute of Medicine and the American Society of Parenteral and Enteral Nutrition (ASPEN). The marketed unapproved TE products contain variable doses that may not be compatible with ASPEN recommendations; these products also have been subject to frequent shortages.

In 2012, ASPEN published a position paper outlining concerns about incorrect dosing and potential contamination of the multi-TE products, including neonatal and pediatric formulations. ASPEN emphasized the need for new products in the market, that conform with clinical guidelines for TE concentrations.[1]

Available Products for Neonates and Young Infants

Marketed Unapproved Products

Multitrace-4-Neonatal is unapproved and marketed by American Regent, the same Sponsor for the Tralement NDA. Each mL of Multitrace-4-Neonatal contains 1.5 mg zinc, 0.1 mg copper, 25 mcg manganese, and 0.85 mcg chromium. This is the only neonatal multiple TE formulation marketed in the U.S.

American Regent also markets:

- Multitrace-4-Pediatric, which contains 1 mg zinc, 0.1 mg copper, 25 mcg manganese, and 1 mcg chromium per mL.
- Manganese sulfate, which is labeled for pediatric patients at a dose of 2 – 10 mcg/kg/day in TPN.

FDA-Approved Products

FDA approved single-element products, selenious acid (April 30, 2019) and zinc sulfate (July 18, 2019), with labeling that included dosing across the entire age range including preterm neonates. Copper is approved as cupric chloride injection, with pediatric labeling. Cupric sulfate has been discontinued.

PRODUCT DESCRIPTION:

Each mL of Tralement™ contains zinc 3 mg (equivalent to zinc sulfate 7.41 mg), copper 0.3 mg (equivalent to cupric sulfate 0.75 mg), manganese 55 mcg (equivalent to manganese sulfate 151 mcg), selenium 60 mcg (equivalent to selenious acid 98 mcg) and water for injection. Sulfuric acid may be added to adjust pH between 1.5 and 3.5.

(b) (4)

DOSING CONSIDERATIONS FOR TRACE ELEMENTS IN TRALEMENT™:

Selenious acid and zinc sulfate were approved in 2019, and therefore, a discussion of specific considerations for selenium and zinc, including deficiency and toxicity will be deferred.

Zinc

The appropriate doses for zinc were established in labeling for the approved product, zinc sulfate.

- Preterm neonates (< 3 kg): 400 mcg/kg/day
- Term neonates (3 kg - <5 kg): 250 mcg/kg/day
- Pediatric patients (5 kg- <10 kg): 100 mcg/kg/day
- Pediatric patients (>10 kg): 50 mcg/kg/day up to a maximum of 3 mg/day

Selenium

The appropriate doses for selenium were established in labeling for the approved product, selenious acid.

- Pediatric patients weighing < 7 kg: 2-4 mcg/kg day
- Pediatric patients weighing ≥ 7 kg: 2 mcg/kg/day up to a maximum of 60 mcg/day

Manganese

Manganese (Mn) is a cofactor for enzymatic processes, and is essential for energy generation, macronutrient metabolism, glucose regulation, neuronal function, and numerous other physiological needs. Though rare, Mn deficiencies can cause significant problems with growth and metabolism. For pediatric patients under 40 kg who are not able to absorb enteral feeding, **Mn supplementation of ~1 mcg/kg/day** is typically added to parenteral nutrition (PN). This dose is recommended by ASPEN and is the maximum dose recommended by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).

1. Vulnerabilities and dosing challenges

PN additives aside from TE preparations may be contaminated with elements such as Mn, further complicating dose recommendations and increasing the potential for toxicity.[2] In a Salt Lake City academic children's hospital, investigators performed a retrospective review of pediatric patients who had received exclusive PN (2007-13) and had either Mn or Se levels drawn. In their review, 561 pediatric patients had received Mn supplementation at 1 mcg/kg/day and 36 patients had not. (The reference range for serum Mn was 4.2-16.5 mcg/L.) Patients weighing <5 kg had mean Mn level 15 +/- 8 mcg/L; with 93% of patients having either acceptable (64%) or high (29%) serum levels. Non-supplemented patients <5 kg also had a mean Mn level of 15 mcg/L, and while 14% of the non-supplemented infants had low levels, 41% had high levels (>16.5 mcg/L).[3] This study, though limited by its use of retrospective review data, illustrates dosing challenges in neonates and young infants.

Elevated Mn levels may occur in the setting of decreased biliary excretion, which is a comorbidity of prolonged parenteral nutrition[4] and of other neonatal conditions with hepatic compromise, including intrauterine growth restriction, anatomical abnormalities such as biliary atresia,[5] chromosomal abnormalities, and congenital viral infections such as cytomegalovirus (CMV).

Elevated Mn levels also may occur with iron (Fe) deficiency, another frequent comorbidity in chronically-ill and parenterally-fed pediatric patients. An increase in transferrin receptors, present at the blood-brain barrier (BBB) mediates brain influx of both Mn and Fe,[6-8] contributing to potential neurotoxic effects. In a U.K. cohort of 36 pediatric patients receiving ≤1 mcg/kg/day of Mn in parenteral nutrition, 9 (25%) had whole blood Mn levels that exceeded reference ranges, up to 16 times the upper limit. Four of the 9 patients had low mean corpuscular volume (MCV), indicating iron deficiency.[9]

Elevated Mn blood levels in the setting of Fe deficiency also may result from environmental and/or dietary exposures (e.g. infants who did not receive parenteral nutrition).[10,11]

2. Toxicities

The following toxicities were found in the literature, searching PubMed for "manganese neurotoxicity," limited to "child: birth to 18 years."

Case reports and cohorts in the adult and pediatric populations contain evidence of:

1. **Clinical signs and symptoms of CNS toxicity** associated with both excess parenteral[12-14] and environmental[15-18] manganese long-term exposure with or without elevated blood levels.[19]
2. **Specific, consistent neuroimaging** in both adults and pediatric patients—MRI findings of increased signal in the basal ganglia on T1-weighted imaging have been associated with excessive manganese exposure[12,14,20-23] with resolution after removal of manganese from PN solutions.[13,24-26]

One case report described a previously healthy 5-year-old with Mn toxicity from well water. She developed abnormal gait, emotional lability, behavior changes, and pica which were associated with increased basal ganglia signal on T1 weighted images.[18]

A randomized controlled study of 2 doses of manganese in neonatal PN, either 1 µmol/kg/d=55 µg/kg/day (group 1, n = 121) or 0.0182 µmol/kg/d=1 µg/kg/day (group 2, n = 123) showed that of neonates who received more than 3/4 of their daily fluid as PN for at least 14 days, neonates on the higher dose developed significantly higher direct bilirubin levels as well as higher serum and whole blood Mn levels.[27]

3. Deficiencies

The following deficiencies were found in the literature, searching PubMed for "manganese deficiency," limited to "child: birth to 18 years."

There are no reports of clinical Mn deficiency in infants on PN. Mn deficiency is exceedingly rare in humans.

Copper

Copper (Cu) is an essential trace element, required for key physiologic enzymes involved in energy metabolism, connective tissue synthesis, iron metabolism and hemoglobin synthesis, free radical scavenging, and catalysis of dopamine to norepinephrine, among other functions. Copper turnover is managed by the liver, including absorption, distribution, and excretion.[28,29] Requirements for dietary copper for term and preterm neonates are variable across the literature. For neonates and infants on PN, the recommended Cu intake is 20 mcg/kg/day.[30]

1. Vulnerabilities and Dosing Challenges

The majority of fetal Cu stores are accumulated in the third trimester of pregnancy; therefore prematurity is a risk factor for Cu deficiency.[31,32] Supplementation in PN is critical for neonates receiving no or partial enteral nutrition.[33,34] In neonates and infants with bowel conditions, absorption also may be impacted.[35-37]

Cu is mainly excreted in bile, therefore it is thought to accumulate in the livers of patients with cholestasis. Conversely, Cu may have a protective effect against PN-induced liver damage. In neonatal and pediatric patients on PN with cholestasis, the practice of reducing Cu supplementation is prevalent, but recent studies suggest that Cu supplementation should be continued, with close monitoring, to avoid deficiencies.[38-43]

2. Toxicities

The following deficiencies were found in the literature, searching PubMed for "copper toxicity AND nutrition," limited to "child: birth to 18 years."

Reports of Cu toxicity in the literature are rare and typically related to contaminated drinking water sources.[44]

3. Deficiencies

The following deficiencies were found in the literature, searching PubMed for "copper deficiency parenteral nutrition," limited to "child: birth to 18 years."

Multiple case reports and case series describe children with anemia, bicytopenia, and/or pancytopenia, and myelodysplastic syndromes with Cu deficiencies.[31,45-47] Because of the necessity of Cu for connective tissue synthesis, deficiencies can also cause growth retardation and poor weight gain, abnormal wound healing, and metabolic bone disease.[48-53]

(b) (4)

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RECOMMENDATIONS:

As currently formulated, Tralement™ does not provide appropriate dosing in any weight band or dose below 55 kg. If dosed so that a pediatric patient receives no more than (b) (4) mcg/kg/day of manganese, the remaining trace elements may be able to be supplemented with FDA-approved products, but such a strategy increases the possibility of dosing errors. A neonatal formulation must be developed, as the currently available marketed unapproved product contains chromium, which is not required, and contains amounts of manganese likely to result in excessive doses.

(b) (4)

[redacted]

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date:	March 31, 2020
Reviewer:	Jamie Ridley Klucken, PharmD, MBA, BCPS, BCACP Safety Evaluator, Division of Pharmacovigilance I (DPV-I)
Team Leader:	Lisa Harinstein, PharmD, BCCCP DPV-I
Associate Division Director:	Eileen Wu, PharmD DPV-I
Product Name:	Tralement (Trace Elements Injection-4)
Subject:	Postmarketing Adverse Events
Application Type/Number:	NDA 209376
Applicant/Sponsor:	American Regent, Inc.
OSE RCM #:	2019-1891

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This pharmacovigilance review, completed by the Division of Pharmacovigilance I (DPV-I) in response to a consult from the Division of Gastroenterology and Inborn Errors Products (DGIEP), contains an analysis of all adverse events associated with marketed unapproved Multi-Trace Element (MTE) Injections or other zinc, copper, manganese, and selenium products in the FDA Adverse Event Reporting System (FAERS) database, the Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS) database, and the medical literature. This review will inform DGIEP as they conduct a standard review of a literature-based 505(b)2 New Drug Application (NDA) for Trace-Elements (TEs) Injection-4 submitted by the Applicant, American Regent, Inc., to FDA on September 5, 2019.

TEs Injection-4 contains zinc sulfate (3 mg), cupric sulfate (0.3 mg), manganese sulfate (55 mcg), and selenious acid (60 mcg). TEs Injection-4 is proposed to be indicated as a source of zinc, copper, manganese, and selenium in parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated.

Of note, DPV-I recently (2019) completed postmarketing reviews for zinc sulfate and selenium. Findings from searching the FAERS database, CAERS database, and medical literature included hypersensitivity events with zinc-containing products, cardiac failure with a fatal 1000-fold overdose of zinc sulfate in an infant, and mild adverse events (e.g., GI symptoms, paresthesia, alopecia, fingernail loss, signs of thyroid deficiency) with high doses of selenium that appeared to be reversible upon discontinuation.

Copper

We identified one FAERS case that described a 2-year-old child who developed elevated transaminases following 13 months of subcutaneous cupric chloride administration. The copper dose was within the recommended dosage range for the indication of Menkes disease, however, the case lacked pertinent details such as baseline liver function.

We identified ten cases in the medical literature describing adverse events following ingestion of unknown (n=5) or higher than recommended doses (n=5, range 9- to 278-fold higher) of oral copper sulfate. The adverse events described include various gastrointestinal, hematologic, renal, hepatic, and respiratory complications as well as rhabdomyolysis, weakness/fatigue, and cardiac arrest. We also identified one case in the medical literature describing similar adverse events following parenteral administration of a 100-fold higher than recommended dose of copper sulfate.

We identified 14 cases in the medical literature (n=8) and FAERS database (n=6) describing systemic hypersensitivity events such as rash, pruritis, urticaria, and angioedema following insertion of a copper intrauterine device (IUD). Many cases described a positive dechallenge (n=11) and/or a positive scratch test to copper (n=7).

Manganese

The FAERS search identified two cases of manganese toxicity with parenteral administration of manganese. One case described Parkinson-like symptoms and positive imaging following

administration of total parenteral nutrition containing manganese at an unknown dose for an unknown duration. The second case described positive imaging following an 8000-fold overdose of manganese due to a compounding error; the patient did not display neurological symptoms despite magnetic resonance imaging (MRI) findings remaining positive for nearly 11 months.

The CAERS database search retrieved 3 cases describing neuropsychiatric adverse events (e.g., stuttering, slurring, headaches, agitation, anxiety, tremors, ataxia, sleep disruption) following ingestion of oral manganese supplementation at unknown (n=1) or 18- to 67-fold higher than recommended doses (n=2) over an average of 4.5 weeks (range 2.5 to 8 weeks).

The medical literature search identified 10 cases describing adverse events with parenteral administration of manganese at unknown (n=1) or 2.7- to 80-fold higher than recommended doses (n=9) administered over an average of 10 months (range 9 days to 4 years), of which a subset (n=7) had underlying hepatic dysfunction, biliary dysfunction, or both. The adverse events described include positive MRI findings (e.g., high-intensity signal on T1-weighted images of the globus pallidus) and neuropsychiatric complications (e.g., confusion, psychomotor retardation, gait disturbance, parkinsonism, and seizures). Notably, in patients reporting dechallenge information (n=9), most noted improvement or resolution of symptoms (7 of 9) and MRI lesions (4 of 5), following manganese discontinuation.

Selenium

We identified five additional cases of adverse events related to selenium supplementation in the updated search of the medical literature (n=3) and the CAERS database (n=2). Four cases described known adverse events associated with selenium toxicity (e.g., GI symptoms, fatigue, alopecia, fingernail changes, and paresthesia) following ingestion of higher than recommended doses of oral selenium supplementation. The remaining single article described new adverse events associated with selenium toxicity such as leukoencephalopathy with progressive cognitive impairment and visual loss, reversible upon discontinuation. However, this case lacked typical adverse events associated with selenium toxicity and was unable to exclude the possibility of contaminants.

Zinc Sulfate

The updated FAERS, CAERS, and medical literature searches did not identify additional cases of adverse events related to zinc sulfate.

Based on this review, DPV-I recommends the following changes to the draft labeling for TEs Injection-4. Notably, these recommendations are not based on any fixed-dose combination products.

- Addition of the single reported case of overdosage with parenteral copper to the OVERDOSAGE section.
- Description of the hypersensitivity events with copper IUDs to the WARNINGS AND PRECAUTIONS and Postmarketing Experience sections.
- Description of the risk of manganese accumulation with hepatic/biliary dysfunction to the WARNINGS AND PRECAUTIONS section.

- Inclusion of neuropsychiatric events and CNS deposition with manganese toxicity to the WARNINGS AND PRECAUTIONS, Postmarketing Experience, and OVERDOSAGE sections.

1 INTRODUCTION

This pharmacovigilance review, completed by the Division of Pharmacovigilance I (DPV-I) in response to a consult from the Division of Gastroenterology and Inborn Errors Products (DGIEP), contains an analysis of all adverse events associated with marketed unapproved Multi-Trace Element (MTE) Injections or other zinc, copper, manganese, and selenium products in the FDA Adverse Event Reporting System (FAERS) database, the Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS) database, and the medical literature. This review will inform DGIEP as they conduct a standard review of a literature-based 505(b)2 New Drug Application (NDA) for Trace-Elements (TEs) Injection-4.

1.1 BACKGROUND[a] AND REGULATORY HISTORY

A 505(b)2 NDA for TEs Injection-4 was submitted by the Applicant, American Regent, Inc., to FDA on September 5, 2019. TEs Injection-4 contains zinc sulfate (3 mg), cupric sulfate (0.3 mg), manganese sulfate (55 mcg), and selenious acid (60 mcg). TEs Injection-4 is proposed to be indicated as a source of zinc, copper, manganese, and selenium in parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated.[1]

TEs are minerals present at very low concentrations in humans. TEs are found in a variety of foods and are essential for certain metabolic and enzymatic functions. Deficiencies in TEs may result in serious adverse clinical outcomes, which have been reported when TEs have been excluded from PN.[2] Table 1 below provides a summary of biological functions and signs and symptoms of deficiency and toxicity for the individual TEs contained in TEs Injection-4.

Table 1. Summary of TE Functions, Deficiencies, and Toxicities[a]

Trace Element	Biological Functions	Deficiency	Toxicity
Copper[3]	- Component of catalytic metalloenzymes - Role against oxidative damage with superoxide dismutases	- Anemia (reduction in neutrophils) - Impaired growth - Osteoporosis - Increased infection - Altered cardiac rhythm - Neurological abnormality	- Nausea, vomiting, diarrhea - Headache - Hemolytic anemia, gastrointestinal bleed - Liver and kidney failure
Manganese[4]	- Bone mineralization - Protein and energy metabolism - Cellular protection from damaging free radicals	- Delayed blood clotting - Hypocholesterolemia - Skin/nail/hair changes - Irregularities in bone calcification	- Neurotoxicity[*]
Selenium[5]	- Synthesis of 35 selenoproteins - Oxidative stress - Thyroid function - Vitamin C metabolism	- Cardiomyopathy - Myopathy - Skin/hair/nail changes - Growth retardation (infants)	- Alopecia - Brittle hair and nails - Nausea, vomiting, garlic breath - Nervous system abnormalities

[a] Adapted from the backgrounder prepared for the Medical Policy & Program Review Council meeting on February 27, 2019, regarding TEs.

Zinc[6,7,8,9]	- Catalyzes enzyme activities - Maintains structural conformations - Mediates regulatory responses	Severe: - Life-threatening Mild: - Diarrhea - Growth retardation - Eye and skin lesions	- Nausea, vomiting, diarrhea, cramps - Decreased copper and iron absorption leading to anemia, leukopenia, myeloneuropathy†
* Chronic liver disease leads to decreased manganese elimination in the bile, increasing the risk of manganese neurotoxicity. † This mechanism of decreased copper absorption is utilized in the treatment of Wilson's disease. Wilson's disease is a rare genetic disorder that results in copper build up in the body, manifesting as neurologic disease and chronic liver disease leading to cirrhosis, which can be fatal.[10]			

DGIEP consulted DPV-I on September 16, 2019, to evaluate postmarketing adverse event reports in the FAERS database and medical literature with MTE supplementation, including zinc sulfate, cupric sulfate, manganese sulfate, and selenious acid to inform DGIEP as they review the ADVERSE REACTIONS *Postmarketing Experience* section of the proposed product label[11] submitted as part of the 505(b)2 NDA submission for TEs Injection-4.

DPV-I previously conducted pharmacovigilance reviews for the approval of Zinc Sulfate Injection (NDA 209377) and Selenious Acid Injection (NDA 209379). The review for Zinc Sulfate Injection[12], completed on June 24, 2019, did not identify any postmarketing reports of zinc-related adverse events in patients receiving intravenously administered PN solutions containing zinc sulfate within the recommended dosage range. However, multiple adverse events (e.g., hypocupremia, hypersensitivity, overdosage-related cardiac failure) were identified with various zinc preparations (e.g., oral, parenteral, hemodialysis fluids, zinc-containing insulin), especially when used at high doses. The review for Selenious Acid Injection[13], completed on March 12, 2019, did not identify any postmarketing reports of selenium-related adverse events associated with standard recommended doses of selenium. Cases reporting high doses of selenium intake reported mild adverse events (e.g., gastrointestinal (GI) symptoms, paresthesia, alopecia, fingernail loss, signs of thyroid deficiency) that appeared to be reversible upon discontinuation.

1.2 REGULATORY HISTORY

MTE solutions for injection are available in the United States as unapproved products produced by American Regent, as listed below. MTE-4 and MTE-5 contain zinc, copper, manganese, and chromium; MTE-5 also contains selenium.

- MTE-4 (NDC Code 0517-7410-25)[14] is available as a 10 mL multiple dose vial
- MTE-4 Neonatal (NDC Code 0517-6202-25)[15] is available as 2 mL single dose vial
- MTE-4 Pediatric Concentrate vial (NDC Code 0517-9203-25)[16] is available as a 3 mL single dose vial
- MTE-4 Concentrate is available as a 1 mL single dose vial (NDC Code 0517-7201-25) and a 10 mL multiple dose vial (NDC Code 0517-7210-25)[17]
- MTE-5 (NDC Code 0517-8510-25)[18] is available as a 10 mL multiple dose vial
- MTE-5 Concentrate is available as a 1 mL single dose vial (NDC Code 0517-8201-25) and a 10 mL multiple dose vial (NDC Code 0517-8210-25)[19]

Individual TE solutions for injection are available in the United States, as listed below. Copper is FDA-approved for use as a supplement to intravenous (IV) solutions given for total parenteral

nutrition (TPN) to maintain copper serum levels and to prevent depletion of endogenous stores and subsequent deficiency symptoms. Zinc and selenium are FDA-approved for use as a source of TE in PN when oral or enteral nutrition is not possible, insufficient, or contraindicated. Manganese is available as an unapproved product.

- Cupric Chloride Injection (NDA 018960)[20] is available through Hospira as a 10 mL vial (0.4 mg/mL)
- Manganese Chloride Injection (NDC Code 0409-4091-01)[21] is available through Hospira as a 10 mL vial (0.1 mg/mL)
- Manganese Sulfate Injection (NDC Code 0517-6410-25)[22] is available through American Regent as a 10 mL vial (0.1 mg/mL)
- Selenious Acid Injection (NDA 209379, approved April 30, 2019)[23] is available through American Regent as a 10 mL vial (60 mcg /mL of selenium)
- Zinc Chloride Injection (NDA 018959, approved June 26, 1986)[24] is available through Hospira as a 10 mL vial (1 mg/mL)
- Zinc Sulfate Injection (NDA 209377, approved July 18, 2019) is available through American Regent as a 10 mL vial (3 mg/mL) and a 5 mL vial (5 mg/mL)[25]

See Appendix A for a list of parenteral TE recommendations and concentrations in available products.

1.3 Relevant Product Labeling

The Applicant's proposed product label for NDA 209376 TEs Injection-4[11] contains the following select safety information below. Select safety information from the approved Zinc Sulfate Injection (NDA 209377), Cupric Chloride Injection (NDA 018960), and Selenious Acid Injection (NDA 209379) product labels as well as safety information from the marketed unapproved Manganese Sulfate Injection (NDC Code 0517-6410-25) product label are listed in Appendix B.

> 4 CONTRAINDICATIONS
>
> Tralement is contraindicated in patients with known hypersensitivity to zinc, copper, (b) (4) *[see Warnings and Precautions (5)]*.
>
> (b) (4)
>
> 5 WARNINGS AND PRECAUTIONS
>
> 5.1 Pulmonary Embolism due to Pulmonary Vascular Precipitates
> Pulmonary vascular precipitates causing pulmonary vascular emboli and pulmonary distress have been reported in patients receiving parenteral nutrition. The cause of precipitate formation has not been determined in all cases; however, in some fatal cases, pulmonary emboli occurred as a result of calcium phosphate precipitates. Precipitation has occurred following passage through an in-line filter; in vivo precipitate formation may also have occurred. If signs of pulmonary distress occur, stop the parenteral nutrition infusion and initiate a medical

evaluation. In addition to inspection of the solution *[see Dosage and Administration (2.2, 2.3)]*, the infusion set and catheter should also periodically be checked for precipitates.

5.2 Vein Damage and Thrombosis

Tralement must be prepared and used as an admixture in parenteral nutrition solutions. It is not for direct intravenous infusion. In addition, consider the osmolarity of the final parenteral nutrition solution in determining peripheral versus central administration. Solutions with an osmolarity of 900 mOsm/L or greater must be infused through a central catheter *[see Dosage and Administration (2.1)]*. The infusion of hypertonic nutrient solutions into a peripheral vein may result in vein irritation, vein damage, and/or thrombosis. The primary complication of peripheral access is venous thrombophlebitis, which manifests as pain, erythema, tenderness or a palpable cord. Remove the catheter as soon as possible, if thrombophlebitis develops.

5.3 Aluminum Toxicity

Tralement contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Patients with impaired kidney function, including preterm infants, can accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

Exposure to aluminum from Tralement is not more than 0 (b) (4) mcg/kg/day. When prescribing Tralement for use in parenteral nutrition containing other small volume parenteral products, the total daily patient exposure to aluminum from the admixture should be considered and maintained at no more than 5 mcg/kg/day *[see Use in Specific Populations (8.4)]*.

5.4 Monitoring and Laboratory Tests

Monitor zinc, copper, selenium, and manganese concentrations, fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, blood count, and coagulation parameters throughout treatment *[see Dosage and Administration (2.4)]*.

(b) (4)

5.6 Hypersensitivity Reactions

If hypersensitivity reactions occur, discontinue Tralement and initiate appropriate medical treatment *[see Contraindications (4)]*.

6 ADVERSE REACTIONS

(b) (4)

(b) (4)

The following adverse reactions were identified in clinical studies or post-marketing reports. Given that some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Adverse reactions with (b) (4) other components of parenteral nutrition solutions:

- Pulmonary embolism due to pulmonary vascular precipitates *[see Warnings and Precautions (5.1)]*
- Vein damage and thrombosis *[see Warnings and Precautions (5.2)]*
- Aluminum toxicity *[see Warnings and Precautions (5.3)]*

(b) (4)

2 METHODS AND MATERIALS

2.1 CAUSALITY ASSESSMENT

Reports were assessed for a causal relationship between the adverse events and zinc sulfate, copper, manganese, and selenium supplementation using a modified version of the World Health Organization-Uppsala Monitoring Center (WHO-UMC) causality assessment tool (see Table 2). Reports assessed as "unassessable" or "unlikely" were excluded from further review.

Table 2. Causality Classification and Criteria based on the WHO-UMC System[26]

Causality Term	Assessment Criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

2.2 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in Table 3.

Table 3. FAERS Search Strategy*	
Search 1: Copper Products	
Date of Search	January 10, 2020
Time Period of Search	All reports through January 9, 2020
Search Type	Quick Query
Product Terms	Product Active Ingredients (PAIs): copper†, copper gluconate, copper/cupric chloride, cupric cation, cupric chloride, cupric chloride anhydrous CU-64, cupric oxide, cupric sulfate, cupric sulfate anhydrous, cupric sulfate CU-64
Search 2: Manganese Products	
Date of Search	January 9, 2020
Time Period of Search	All reports through January 8, 2020
Search Type	Quick Query
Product Terms	Product Name: manganese PAIs: manganese carbonate, manganese chloride, manganese citrate, manganese gluconate, manganese glycerophosphate, manganese sulfate, manganese sulfate anhydrous
Search 3: Selenium Products	
Date of Search	January 9, 2020
Time Period of Search	February 22, 2019 to January 8, 2020‡
Search Type	Quick Query
Product Terms	PAIs§: selenious acid, selenium, selenomethionine, selenomethionine SE-75, sodium selenide, sodium selenate, sodium selenite
Search 4: Zinc Sulfate Products	
Date of Search	January 9, 2020
Time Period of Search	May 2, 2019 to January 8, 2020‡
Search Type	Quick Query
Product Terms	PAIs:‖ zinc sulfate heptahydrate; zinc sulfate monohydrate; zinc sulfate, unspecified form
Search 5: Multi-trace Products	
Date of Search	January 10, 2020
Time Period of Search	All reports through January 9, 2020†
Search Type	Quick Query

Table 3. FAERS Search Strategy*	
Product Terms	PAIs¶: chromic chloride\cupric chloride\manganese chloride\zinc chloride, chromic chloride\cupric sulfate\manganese sulfate\zinc sulfate heptahydrate, chromic chloride\cupric sulfate\manganese sulfate\selenious acid\zinc sulfate heptahydrate

* See Appendix C for a description of the FAERS database.
† The copper PAI identified reports related to copper intrauterine devices. The reports described adverse events such as device issues (e.g., device breakage, embedded device, device dislocation) and local issues (e.g., pain, bleeding); therefore, only a targeted search of hypersensitivity events with this PAI was performed because hypersensitivity to copper was included as a contraindication for use in the proposed TEs Injection-4 label.
‡ Update to the previous DPV-I review which conducted a FAERS search through February 21, 2019, for selenium products and through May 1, 2019, for zinc sulfate products.
§ The selenomethionine PAI was not included in DPV's previous review; a FAERS search through February 21, 2019, the search dates from the previous review, did not identify any reports with this PAI. The selenium sulfide PAI was excluded from the search because it identified reports related to topical prescription preparations (e.g., lotion or shampoo) indicated for the treatment of dandruff and seborrheic dermatitis.
|| The zinc sulfate\zinc sulfate anhydrous PAI included in DPV's previous review is no longer an available PAI.
¶ The MTE PAIs included in this search are not the same combination of TEs included in Tralement.

2.3 CAERS SEARCH STRATEGY

DPV-I searched the CAERS database with the strategy described in Table 4.

Table 4. CAERS Search Strategy	
Search 1: Copper Products	
Date of Search	February 18, 2020
Time Period of Search	All reports through February 17, 2020
Search Type	PRIMO
Product Terms	Product Name contains: "copper" or "cupric"
Search 2: Manganese Products	
Date of Search	February 19, 2020
Time Period of Search	All reports through February 18, 2020
Search Type	PRIMO
Product Terms	Product Name contains: "manganese"
Search 3: Selenium Products	
Date of Search	February 25, 2020
Time Period of Search	February 26, 2019 to February 24, 2020†
Search Type	PRIMO
Product Terms	Product Name contains: "selenium"
Search 4: Zinc Sulfate Products	
Date of Search	February 25, 2020
Time Period of Search	May 6, 2019 to February 24, 2020†
Search Type	PRIMO

Table 4. CAERS Search Strategy	
Product Terms	Product Name contains: "zinc"
Search 5: Multi-trace Products	
Date of Search	February 26, 2020
Time Period of Search	All reports through February 25, 2020
Search Type	PRIMO
Product Terms	Product Name contains: "multitrace", "multi-trace"
* See Appendix B for a description of the CAERS database. † Update to the previous DPV-I review which conducted a CAERS search through February 25, 2019, for selenium products and through May 5, 2019, for zinc sulfate products.	

2.4 LITERATURE SEARCH

DPV-I searched the medical literature with the strategy described in Table 5.

Table 5. Literature Search Strategy	
Date of Search	February 3, 2020
Database	Embase, PubMed@FDA

Table 5. Literature Search Strategy	
Search Terms*	Embase Searches: 1. 'copper sulfate' AND ('adverse drug reaction'/exp OR 'adverse drug reaction' OR 'toxicity'/exp OR toxicity) AND ('case report'/exp OR 'case report') 2. 'manganese' AND ('adverse drug reaction'/exp OR 'adverse drug reaction' OR 'toxicity'/exp OR toxicity) AND ('case report'/exp OR 'case report') AND 'total parenteral nutrition' 3. ('selenious acid'/exp OR 'selenious acid' OR 'selenium'/exp OR 'selenium') AND ('adverse drug reaction'/exp OR 'adverse drug reaction' OR 'toxicity'/exp OR toxicity) AND ('case report'/exp OR 'case report') 4. ('zinc'/exp OR zinc) AND ('adverse drug reaction'/exp OR 'adverse drug reaction' OR 'toxicity'/exp OR toxicity) AND ('case report'/exp OR 'case report') 5. 'trace element' AND ('adverse drug reaction'/exp OR 'adverse drug reaction' OR 'toxicity'/exp OR toxicity) AND ('case report'/exp OR 'case report') PubMed Searches: 1. copper sulfate AND (Adverse Drug Reaction OR Toxicity) AND (Case Report) 2. manganese AND (Adverse Drug Reaction OR Toxicity) AND (Case Report) AND (parenteral nutrition) 3. (selenium OR selenious acid) AND (Adverse Drug Reaction OR Toxicity) AND (Case Report) 4. (zinc sulfate) AND (Adverse Drug Reaction OR Toxicity) AND (Case Report) 5. (trace element) AND (Adverse Drug Reaction OR Toxicity) AND (Case Report) AND (parenteral nutrition) 6. copper AND hypersensitivity AND intrauterine device†
Years Included in Search	All‡

* The search terms TPN or PN were added to some TE searches to exclude irrelevant reports related to environmental exposure.
† A targeted search of hypersensitivity events with copper intrauterine devices was performed on March 13, 2020, because hypersensitivity to copper was included as a contraindication for use in the proposed TEs Injection-4 label.
‡ For zinc sulfate and selenious acid, we analyzed articles published since the previous reviews; search dates May 21, 2019, and February 25, 2019, respectively.

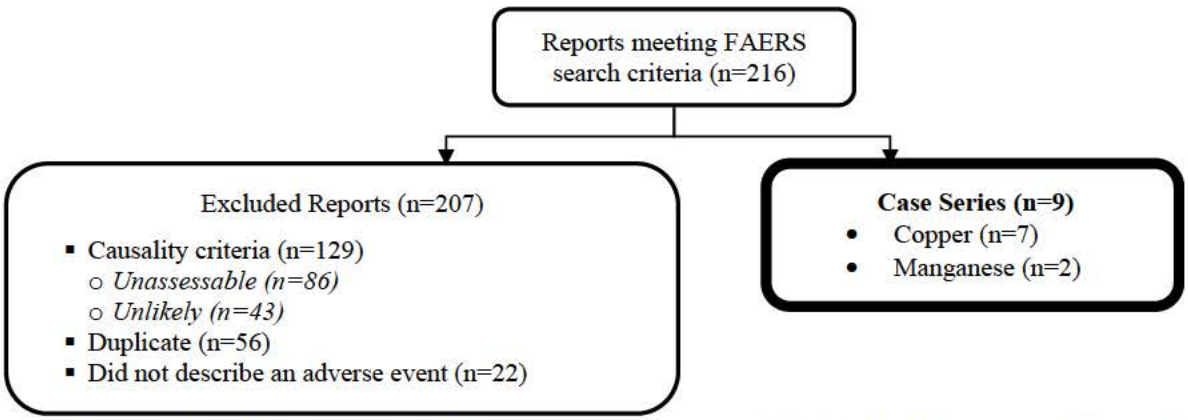
3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS searches retrieved 216 reports with copper products (n=102), MTE products (n=74), manganese products (n=20), selenium products (n=15), or zinc sulfate products (n=5). After accounting for duplicate reports (n=56), 120 reports were analyzed for inclusion in the case series of adverse events reported with zinc sulfate, copper, manganese, selenium, or MTE use. After applying WHO-UMC causality criteria, nine reports were included in the case series (see

Figure 1 for details of the FAERS case selection, see Appendix C for a line listing of the cases included in the case series).

Figure 1. FAERS Case Selection



*Reports were deemed unlikely for the following reasons: symptoms related to TE deficiency, underlying disease, or a procedure; events occurred prior to TE/PN administration; or concomitant medication(s), product contamination, or a medication error provide a likely alternative explanation.

The nine cases in the FAERS case series reported the following adverse events: hypersensitivity events following insertion of a copper intrauterine device (IUD), elevated transaminases with subcutaneous copper supplementation, Parkinson-like symptoms and positive magnetic resonance imaging (MRI) findings with IV manganese supplementation, and positive MRI findings without associated symptoms following a massive manganese overdose. These cases are further described below.

3.1.1 Copper Cases (n=7)

- ***Hypersensitivity (n=6)***

We identified six cases of hypersensitivity events (e.g., rash, hives, and pruritis) following insertion of a copper IUD. Four of the cases reported a positive dechallenge with resolution of symptoms after removal of the IUD. None of the cases reported a positive copper scratch test to confirm a copper allergy.

Reviewer's comment: The TEs Injection-4 proposed product label contains a contraindication for use in patients with hypersensitivity to copper. These cases demonstrate the potential for systemic hypersensitivity reactions to the copper contained in IUDs. It is notable that two-thirds of the cases reported positive dechallenge, however, none reported performing additional diagnostic testing (e.g., scratch testing).

- ***Elevated Transaminases (n=1)***

FAERS Case #4814923, outcome: other serious, USA, 1991:
A physician reported a 2-year-old male taking cupric chloride L-histidine 1 mL subcutaneously three times weekly for 13 months for Menkes disease experienced elevated transaminases (serum

glutamic pyruvic transaminase 150-250 range, no reference range provided) without coagulopathy or other laboratory abnormalities. The medication was stopped for 8-10 weeks and the transaminases returned to normal. Transaminases increased again after the medication was restarted and the drug was permanently discontinued.

Reviewer's comment: This case describes a 2-year-old child administered cupric chloride 400 mcg[b] subcutaneously three times weekly (approximating 171 mcg daily) for the treatment of Menkes disease, a copper deficiency disorder, who experienced ***elevated transaminases*** *after 13 months of therapy. The case did not provide serum copper concentrations or detailed laboratory data. Current recommendations for Menkes disease include subcutaneous copper-histidine supplementation at a dose of 250 mcg twice daily until the end of the first year of life followed by 250 mcg daily.[27,28] The dose administered represents a dose within the range currently recommended for supplementation[c] and Menkes disease treatment. A positive dechallenge and rechallenge were noted indicating copper supplementation was probably related.*

3.1.2 Manganese Cases (n=2)

FAERS Case #6612496, outcome: life-threatening, other serious, Germany, 2008:
A literature report[29] described a 12-year-old female with acute myelogenous leukemia who underwent an allogeneic, related, matched transplantation from peripheral blood stem cells who experienced graft-vs-host disease grade IV after receiving conditioning treatment with cyclophosphamide, busulfan, and melphalan. The patient developed Parkinson-like symptoms while receiving supplemental manganese with TPN. Imaging revealed a high signal in the globus pallidum and putamen. The cause was listed as manganese toxicity. The authors stated that the supplemental manganese provided in the TPN, coupled with hepatic dysfunction, led to intoxication in the patient.

Reviewer's comment: This case describes manganese toxicity and ***Parkinson-like symptoms*** *following TPN administration with supplemental manganese.* ***Positive MRI results*** *indicate the neurological symptoms are likely related to manganese toxicity. Manganese-induced parkinsonism and central nervous system (CNS) deposition has been reported in patients with chronic liver failure (unable to excrete manganese in bile) or in patients receiving TPN.[30,31,32,33] There is no description of liver disease in this patient, nor details of the manganese dose or serum concentrations.*

FAERS Case #12424592, outcome: hospitalization, other serious, United States, 2016:
A literature report[34] described a 52-year-old female with a past medical history of Hashimoto's thyroiditis (controlled) and perceived heavy metal toxicity (lead concentration 3.0 g/dL). Concomitant medications included a thyroid supplement (unknown dose and duration) and IV chelation therapy for heavy metal toxicity including calcium disodium EDTA 2.5 mg, ascorbic acid, potassium chloride, thiamine, pantothenic acid, pyridoxine hydrochloride, sodium bicarbonate, acetylcysteine, heparin, and glutathione. Additionally, the patient was supposed to

[b] The formulation for cupric chloride is 0.4 mg/mL.
[c] The recommended copper supplementation for neonates, infants, and children without Menkes disease is 20 mcg/kg. An average weight 12-month-old male is 10.5 kg, which would approximate 210 mcg daily; an average weight 24-month-old male is 12.5 kg, which would approximate 250 mcg daily.

receive 800 mg of MAGNESIUM chloride as part of chelation therapy, but instead received 800 mg of MANGANESE chloride intravenously. The patient experienced flushing during administration and arrived at the emergency department (ED) an hour after infusion. Her whole blood manganese concentration obtained six hours after exposure and prior to treatment was elevated (see levels below). Although asymptomatic on initial presentation, the patient underwent two hemodialysis (HD) sessions over 4 hours at 7 and 21 hours after exposure. Following HD, she received five consecutive days of calcium disodium EDTA ($1g/m^2$ over 8 hours) following HD, in an attempt to minimize the risk of manganese deposition in the CNS. Following HD, the manganese concentration decreased, but remained above normal. Analysis of the dialysate from the first HD session revealed total elimination of only 604 mcg of manganese (approximately 1.4% of manganese burden). MRI on hospital day 2 revealed T1 hyperintensities in the bilateral globus pallidi. On day 5, the manganese concentration was within normal limits and she was discharged from the hospital. One month following exposure, MRI results were unchanged. She remained asymptomatic at a 9-month follow-up with stable MRI findings at 11 months.

Date	**Manganese Level* (normal <5 mcg/L)**	**Timing**
Day 1	120 mcg/L	6 hours after exposure, prior to treatment
Day 1	20 mcg/L	after initial HD session (7 hours after exposure)
Day 5	2.2 mcg/L	after 2 HD sessions and 5 days of calcium disodium EDTA therapy
*Manganese blood level determined by inductively coupled plasma mass spectrometry.		

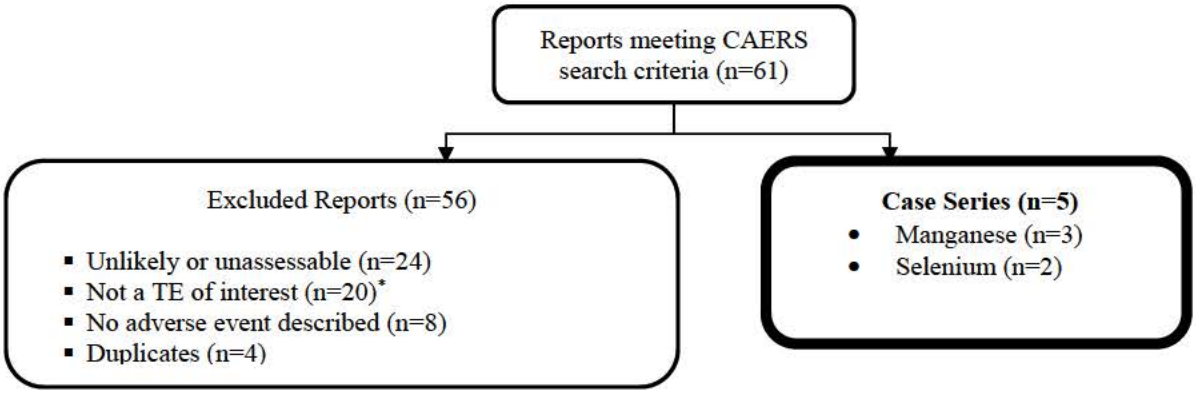
Reviewer's comment: This case describes a medication error that resulted in a patient receiving an 8000-fold overdose of IV manganese.[d] *Her blood manganese levels were 60-fold higher than normal 6 hours after exposure and* ***MRI findings were positive*** *2 days after exposure, although she did not display any neurological symptoms. Although manganese is primarily excreted in the bile, HD was initiated in an attempt to minimize the risk of manganese deposition in the CNS.*[35] *Despite treatment which effectively lowered the patient's manganese levels to the normal range, she continued to have positive MRI findings up to 11 months after the overdose. Positive imaging studies were likely related to manganese toxicity.*

3.2 CAERS DATABASE RESULTS

The CAERS search retrieved 61 reports with copper products (n=32), zinc sulfate products (n=16), manganese products (n=6), selenium products (n=6), or MTE products (n=1). All but 5 reports were excluded from the case series because the product was deemed unlikely or unassessable (n=24), did not contain a TE of interest (n=20), did not describe an adverse event (n=8), or were a duplicate (n=4). See Figure 2 for details of the CAERS case selection and Appendix E for a line listing of reports retrieved in CAERS.

[d] ASPEN recommends parenteral manganese supplementation for adults is 60-100 mcg per day.

Figure 2. CAERS Case Selection



*Reports were not considered a TE of interest for the following reasons: product does not contain TE[e]; TE was a component of a combination product or a topical cosmetic.

The five cases included in the CAERS case series reported adverse events after ingesting higher than recommended doses of oral manganese (n=3) or selenium (n=2) supplements. These cases are further discussed below.

3.2.1 Manganese Cases (n=3)

Case #170513, outcome: hospitalization, required intervention, disability, USA, 2013:
A 47-year-old female with a past medical history of hypothyroidism and magnesium deficiency presented to the ED after inadvertently taking manganese 120 mg daily for 3 weeks, mistaking it for magnesium. Concomitant supplements included vitamins A, C, D, E, fish oil, magnesium, selenium, zinc, probiotics, and "liver, lymph, and kidney support." She reported stuttering, slurring, shaking, terrible headaches, extreme agitation after initiation of manganese, followed by weeks of fatigue. She was diagnosed with manganese toxicity by a neurologist.

Reviewer's comment: This case describes various ***neuropsychiatric adverse events*** *due to manganese toxicity following inadvertent initiation of high doses of manganese supplementation for 3 weeks, rather than magnesium supplementation. The American Society of Parenteral and Enteral Nutrition (ASPEN) recommends manganese 1.8 mg orally daily for adult women, representing a nearly 67-fold higher than recommended oral dose.[39] Notably, only 1 to 5% of dietary manganese is thought to be absorbed and amounts absorbed may vary by age and amount ingested. However, little is known about the mechanisms that control absorption.[4] Therefore, it is difficult to estimate a comparable dose that would be received parenterally.*

Case #2019-CFS-004830[f], outcome: disability, USA, 2019:
A 52-year-old female with a past medical history of hypothyroidism, supraventricular tachycardia, fibromyalgia, low blood pressure, insomnia, anxiety, tardive dyskinesia, interstitial cystitis, and cataracts started manganese 32 mg daily as a holistic treatment for orofacial tardive

[e] Products contained copper in the reported product name but did not contain copper (e.g., Copperstown Cookies, Copper River Seafoods, Copper River Salmon) or were not food or dietary supplements (e.g., copper frying pan).
[f] Duplicate report: Case# 2019-CFS-002120

dyskinesia. Concomitant medications included levothyroxine, fludrocortisone, clonazepam, diltiazem, quetiapine, gabapentin, and various supplements including melatonin, super enzymes, castor oil, magnesium oxide, and a multivitamin. After nearly 8 weeks of manganese supplementation, she complained of ataxia and Parkinson-like tremors. The tremors resolved following discontinuation. About a month after discontinuation, she began stuttering, which progressed to dysphasia and then resolved 3 months later. Although ataxia improved following discontinuation, she still requires a cane to walk.

*Reviewer's comment: This case describes **ataxia and tremors** following 8 weeks of manganese supplementation at nearly 18-fold higher than recommended supplemental oral dose. The patient experienced a positive dechallenge with resolution of tremor and some improvement in ataxia, indicating manganese supplementation was possibly related. Antipsychotic treatment may be a confounder given some symptoms occurred following discontinuation of manganese.*

Case #2019-CFS-009622, outcome: other serious, USA, 2019:
A 56-year-old post-menopausal female with a past medical history of well-controlled Hashimoto's thyroiditis, osteoarthritis, adhesive capsulitis, and chondromalacia of the shoulder started taking manganese-B_{12} 3 to 4 tablets daily for 2.5 weeks. Concomitant medications included multiple herbal supplements (e.g., Ashwagandha complex 1 tablet daily, Ostarplex 1 tablet four times daily, Thytrophin PMG 1 tablet four times daily, Boswellia Complex 1-2 tablets four times daily, Triphala 3000 mg daily, and Relizen)[g], hydroxyzine pamoate 25mg as needed before bedtime, and levothyroxine 0.125 mg daily. She reported a metallic taste and headaches within 10 to 15 minutes of taking the manganese supplement. Subsequently, she reported severe sleep disruption, generalized anxiety, and upper GI distress. She discontinued all medications for 36 hours; she restarted everything but the manganese supplement and had no recurrence of symptoms.

*Reviewer's comment: This case describes **sleep disruption, anxiety, and upper GI symptoms** following 2.5 weeks of manganese supplementation at an unknown dose. The patient experienced a positive dechallenge without recurrence of symptoms despite reinitiation of all other medications and supplements, indicating manganese supplementation was possibly related.*

3.2.2 Selenium Cases (n=2)

Case #2019-CFS-009973, outcome; none reported, USA, 2019
The mother of a 9-year-old female reported that her daughter was started on selenomethionine 200 mcg daily by her doctor for her "sluggish thyroid." Notably, the mother also submitted a report for herself (see Case #2019-CFS-009971/2019-CFS-010031 below). The child had a past medical history of elevated thyroid stimulating hormone; concomitant medications and supplements were not provided. After 1 month of supplementation, she complained of headaches and muscle aches; after another month of supplementation, she began vomiting 10

[g] Ashwagandha Complex claims to contain ashwagandha, licorice, skullcap, and Korean ginseng. Ostarplex claims to contain Betacol, Cal-Amo, Cataplex G, Ostrophin PMG, and Phosfood liquid for bone and connective tissue support. Thytrophin PMG claims to be a natural thyroid extract. Boswellia Complex claims to contain Boswellia, Celery Seed, Ginger and Turmeric. Triphala claims to contain Amla fruit, Bibhitaki fruit, Haritaki fruit, and Vegetable Pullulan for digestive health. Relizen claims to contain flower pollen extract for menopause symptoms.

minutes after administration. She discontinued all supplements and then restarted them all, one by one, as instructed by the doctor. One week after restarting all supplements, she started vomiting again 10 minutes after administration and discontinued use. Shortly thereafter, bloodwork revealed elevated selenium (270 mcg/L, normal 73-178).

Reviewer's comment: This case describes a 9-year-old child reporting ***headaches, muscle aches, and vomiting*** *following administration of a 5-fold higher than recommended dose of oral selenium and other unknown supplements for 2 months. ASPEN recommends 40 mcg selenium orally daily for children 9 to 13 years. Notably, more than 90% of selenomethionine is thought to be absorbed[3]; 200 mcg orally would equate to 180 mcg parenterally, which is 3 times higher than that contained in the proposed product. A positive dechallenge and rechallenge were noted when all supplements were discontinued and restarted. Despite the lack of information about concomitant supplements, elevated selenium levels indicate selenium supplementation is possibly related.*

Case #2019-CFS-009971/2019-CFS-010031, outcome; none reported, USA, 2019
A 39-year-old female with a past medical history of Hashimoto's thyroiditis had been taking selenomethionine 200 mcg daily for years on the advice of her doctor for thyroid disease. Concomitant medications were not provided; patient noted she was supplementing "minerals." She reported "getting worse" over the past year, describing extreme fatigue, nausea, headaches, skin issues, and body odor. Bloodwork revealed elevated selenium (820 mcg/L, normal 110-330).

Reviewer's comment: This case describes a patient reporting ***fatigue, nausea, headaches, abnormal nail growth, eczema, breath odor, and urine odor*** *following years of taking a 3.6-fold higher than recommended dose of selenium for years and other unknown supplements. ASPEN recommends 55 mcg selenium orally daily for adults. Despite the lack of information about concomitant supplements, elevated selenium levels indicate selenium supplementation is possibly related.*

3.3 LITERATURE SEARCH

The literature search identified 32 cases from 30 publications describing toxicity following oral (n=10) and parenteral (n=1) administration of copper, hypersensitivity events following insertion of copper IUDs (n=8), toxicity following parenteral administration of manganese (n=10), and toxicity following oral administration of selenium (n=3).

3.3.1 Copper Cases (n=19)

- ***Toxicity (n=11)***

We identified 11 cases of copper toxicity from 10 publications in the medical literature. Six cases described one-time administration of higher than recommended copper doses, including oral (n=5) and parenteral copper (n=1); the remaining five cases of oral copper ingestion did not report a dose. Cases of oral administration reported ingestion of 8 to 250 mg one-time doses,

representing a 9 to 278-fold higher than recommended oral copper dose.[h] A single case of parenteral copper administration is further described below. See Appendix F for a line listing of medical literature cases reporting copper toxicity with oral ingestion and associated adverse events.

Oldenquist G and Salem M. (1999) Parenteral copper sulfate poisoning causing acute renal failure. Nephrol Dial Transplant. 14: 441-443.

A 47-year-old male without a significant past medical history presented to the ED 3 days after injection of 50 mg copper sulfate intravenously and subcutaneously in a suicide attempt. Within 15 minutes of initial administration he developed **nausea, vomiting, diarrhea, hematemesis, and hematuria.** The following day he was anuric and had diffuse **abdominal pain and myalgia**. The third day he became **jaundiced**, confessed to the injection, and was taken to the hospital by ambulance and noted to be hypotensive with melena and hematemesis. He was admitted with a hemoglobin of 5 g/dL, hematocrit of 9.4%, platelet count of 94,000/cm^3, and CPK of 2528 U/L. He received IV fluids, 3 units of packed red blood cells, and 3 units of fresh frozen plasma. He also received penicillamine 40 mg/kg and dimercaprol 5 mg/kg twice before being transferred to another hospital complaining of **dyspnea** and abdominal pain. Abnormal labs included methemoglobin 6.3%, positive myoglobin, Na 113 mmol/L, Cl 87 mmol/L, HCO_3 19 mmol/L, BUN 194 mg/dL, SrCr 9.8 mg/dL, ALT <9 U/L, AST 300 U/L, total bilirubin 14.6 mg/dL, conjugated bilirubin 8.2 mg/dL, CK 2831 U/L, PaO_2 76 mmHg (room air), $PaCO_2$ 26.5, and pH 7.46.. Vital signs included BP 156/88, pulse 88, T 100.2F, RR 17. Upon admission he was prepared for HD due to **acute renal failure**. EDTA was infused prior to HD on day 1 and day 3. Serum copper levels and dialysate copper concentration were measured (see below). On day 3 his hypotension, hemolysis, and bleeding were stable. Urine output increased and he required only one more hemodialysis after discharge. Six weeks after the injection, his creatinine was 1.7 and he was doing well.

Time	Serum copper		Dialysate copper	
	Pre-dialysis (μg/dl)	Post-dialysis (μg/dl)	Pre-dialysis (μg/l)	Post-dialysis (μg/l)
Day 1	180	165	20	25
Day 3	165	168	28	23

Reviewer's comment: This case describes an intentional one-time 50 mg parenteral dose of copper that resulted in GI symptoms, hematemesis, hematuria, myalgia, dyspnea, acute kidney injury, and liver injury. ASPEN recommends 0.3-0.5 mg parenterally daily for adults, representing a 100-fold higher than recommended parenteral copper dose. The patient demonstrated clinical improvement following HD and chelation therapy.

- ***Hypersensitivity (n=8)***

[h] ASPEN recommends 900 mcg copper orally daily for adults.

We identified eight cases of hypersensitivity events with copper IUDs in the medical literature. See Table 6 for a line listing of medical literature cases reporting hypersensitivity events following insertion of copper IUDs.

Table 6. Medical Literature Cases of Hypersensitivity Events with Copper IUDs

	CITATION	AGE	REACTION	RASH	URTICARIA	ANGIOEDEMA	PRURITIS	POSITIVE COPPER SCRATCH TEST	POSITIVE DECHALLENGE
1	Barranco VP. (1972) Eczematous dermatitis caused by internal exposure to copper. Arch Derm. 106: 386-7.	26	Pruritic dermatitis on arms; diffuse erythematous, maculopapular eruption of the arms and trunk with excoriations that occurred 2 weeks after IUD insertion. Initially treated with topical corticosteroids. One week later she was markedly worse with subacute dermatitis involving most cutaneous surfaces except face, palms, and soles; treated with oral antihistamines and corticosteroid injections. Some improvement noted initially, but a marked flare occurred 10 days later; oral steroids for 10 days added. Severe generalized flare occurred 9 days later.	Y	Y		Y	Y	Y
2	Barkoff JR. (1976) Urticaria secondary to a copper intrauterine device. Int J Dermatol. 15(8): 594-5.	24	Severe acute urticarial reaction, joint pain and marked angioedema 1 month after copper IUD insertion. Improvement over 11 days with high doses of adrenalin, systemic steroids, and antihistamines.		Y	Y		Y	Y
3	Byrnes AJ. (1978) Allergy to copper in intra-uterine devices. Med J Aust. 2(11): 532-3.		Whole body urticarial rash 9 days after IUD insertion. Similar reaction following second IUD insertion (first one expelled). Facial swelling of lips and eyelids after being instructed to tape a piece of copper to her forearm.	Y	Y			*	†
4	Rongioletti F, Rivara G, and Rebora A. (1985) Contact dermatitis to a copper-containing intra-uterine device. Contact Dermatitis. 13(5): 343.	35	Itchy dermatitis on trunk and limbs for 2 months; onset a few weeks after insertion. Transient improvement with antihistamines and local and systemic steroids. Erythematous papulovesicular eruption with excoriations on trunk, thighs, groin, and vulva; whitish vaginal discharge.	Y			Y	Y	Y
5	Siliotti F, Caroti S, Caroti A, Alborino F. (1987) Allergy to a copper-medicated IUD: a case report. Ginecol Clin. 8(3):197-200.	28	Mild eyelid and perioral erythema with itching 2 months after insertion. Acute facial erythema, whole body eruptive erythematous wheels, intense itching, leukorrhea, and pelvic pain 5-6 months after IUD insertion. Regression with antihistamine therapy; relapse with menstruation.		Y	Y	Y	Y	Y
6	Hocher B, Keller F, Krause PH, et al. (1992). Interstitial nephritis with reversible renal failure due to a copper-containing intrauterine contraceptive device. Nephron. 61: 111-113.	41	Admitted to hospital with renal failure after a 2-month history of anorexia, nausea, vomiting, burning feet, and lethargy. Copper IUD inserted 18 months prior; history of nickel and chrome hypersensitivity. A renal biopsy revealed active chronic interstitial nephritis with infiltration by lymphocytes and eosinophilic granulocytes. Hemodialysis (HD) was started. A second renal biopsy revealed progression of interstitial nephritis; steroids were started for 10 days with limited improvement. The IUD was removed 6 weeks after admission; creatinine decreased and HD was discontinued.					Y‡	Y§
7	Purello D'Ambrosio F, Ricciardi L, Isola S, et al. (1996) Systemic contact dermatitis to copper-containing IUD. Allergy. 51(9): 658-9.	32	Widespread urticaria, angioedema of the eyelids and labia, postmenstrual hematic stillicidium and leukorrhea for 6 months; reported copper-containing IUD for past 12 months. Intermittent temporary relief with corticosteroids and antihistamines.		Y	Y		Y‡	Y
8	Pujol RM, Randazzo L, Miralles J, and Alomar A. (1998)	41	Recurrent eruption over past 2 years; appeared 3-7 days before menses and improved spontaneously with onset of bleeding.	Y				Y‖	Y‖

	Perimenstrual dermatitis secondary to a copper-containing intrauterine contraceptive device. Contact Dermatitis. 38: 288.		Non-itchy erythematous papules on upper trunk, neck, and arms associated with abdominal distension and cramps. Copper IUD placed 12 years prior.						

* Copper taped to patient's forearm.
† The original IUD was expelled; an improvement in symptoms was not reported. A positive rechallenge was noted six days after reinsertion.
‡ Patient also had a positive in vitro lymphocyte-stimulating test with copper, with a typical crescendo reaction.
§ Positive dechallenge after IUD removal confounded by a possible delayed response to concomitant steroid therapy.
‖ Patient also tested positive for nickel, ethylenediamine hydrochloride, and cobalt chloride. Abdominal symptoms resolved at the following cycle; the severity and extent of the rash decreased during following cycles.

Reviewer's Comment: In addition to the six FAERS cases, we identified eight cases of systemic hypersensitivity events following copper IUD insertion despite copper's relatively low sensitization potential. [36,37] *Many of the eight literature cases reported systemic symptoms, similar to the FAERS cases, such as urticaria, rash, angioedema, and pruritis. Most medical literature cases reported confirmatory scratch tests (n=7), most reported a positive dechallenge following removal of the IUD (n=7), and one case reported a positive rechallenge following reinsertion of a copper IUD. The FAERS cases lacked confirmatory scratch tests, although many (4 of 6) did report a positive dechallenge. The medical literature case describing interstitial nephritis reported a positive dechallenge that was confounded by initiation of steroid therapy.*

3.3.2 Manganese Cases (n=10)

We identified 10 cases of manganese toxicity from 9 publications in the medical literature. Nine cases described higher than recommended manganese doses; one case did not report a dose. See Table 7 for a line listing of medical literature cases reporting manganese toxicity and associated adverse events (see Appendix F for additional case details).

Table 7. Medical Literature Cases of Manganese Toxicity

	CITATION	AGE	SEX	UNDERLYING HEPATIC DYSFUNCTION	ROUTE	DOSING (mg)	DURATION	POSITIVE MRI	CONFUSION	PARKINSONISM	SEIZURES	SYMPTOM/MRI IMPROVEMENT
1	Walter E, Alsaffar S, Livingstone C, and Ashley SL. (2016) Manganese toxicity in critical care: Case report, literature review and recommendations for practice. J Intensive Care Soc. 17(3): 252-7.	62	M	Bilirubin and ALT elevated following discontinuation; alkaline phosphatase was elevated throughout admission.	IV	0.27	2.5 mo			X		N/NA
2	McKinney AM, Filice RW, Teksam M, et al. (2004) Diffusion abnormalities of the globi pallidi in manganese neurotoxicity. Neuroradiology. 46(4): 291-295.	55	F	Recent liver transplant; liver failure	IV	NR	3 wk	X				*
3	Kamata N, Oshitani N, Oiso, R, et al. (2003) Crohn's disease with parkinsonism due to long-term total parenteral nutrition. Digest Dis Sci. 48(5): 992-4.	53	F	Elevated transaminases 6 years prior; liver function tests normalized after manganese discontinuation.	IV	7.916	48 mo	X	X			N/N

	CITATION	AGE	SEX	UNDERLYING HEPATIC DYSFUNCTION	ROUTE	DOSING (mg)	DURATION	POSITIVE MRI	CONFUSION	PARKINSONISM	SEIZURES	SYMPTOM/MRI IMPROVEMENT
4	Komaki H, Maisawa S, Sugai K, Kobayashi Y, and Hashimoto T. (1999) Tremor and seizures associated with chronic manganese intoxication. Brain and Dev. 21(2): 122-4.	2	F	Mild hepatomegaly	IV	1.1	14 mo	X		X	X	R/R
5	Nagatomo S, Umehara F, Hanada K, et al. (1999) Manganese intoxication during total parenteral nutrition: report of two cases and review of the literature. J Neurol Sci. 162(1): 102-5.	68	F	NR	IV	~1.1	3 mo	X	†	X		I/I
6	Nagatomo S, Umehara F, Hanada K, et al. (1999) Manganese intoxication during total parenteral nutrition: report of two cases and review of the literature. J Neurol Sci. 162(1): 102-5.	70	M	NR	IV	~1.1	2 mo	X	X	X		I/I
7	Fredstrom S, Rogosheske J, Gupta P, and Burns LJ. (1995) Extrapyramidal symptoms in a BMT recipient with hyperintense basal ganglia and elevated manganese. Bone Marrow Transplant. 15: 989-992.	51	F	Cholestasis during hospitalization	IV	0.3	55 d	X		X		I/NR
8	Taylor S and Manara AR. (1994) Manganese toxicity in a patient with cholestasis receiving total parenteral nutrition. Anaesthesia. 49(11): 1013.	44	F	Simultaneously developed obstructive jaundice	IV	2.2	9 d		X	X		R/NA
9	Ejima A, Imamura T, Nakamura S, et al. (1992) Manganese intoxication during total parenteral nutrition. Lancet. 339: 426.	62	M	NR	IV	2.2	23 mo	X		X		I/I
10	Mehta R and Reilly JJ. (1990) Manganese levels in a jaundiced long-term total parenteral nutrition patient: Potentiation of haloperidol toxicity? Case report and literature review. J Parenter Enter Nutr. 14(4): 428-30.	32	F	Progressive hepatic failure; biopsy demonstrated early biliary cirrhosis. Liver function continued to worsen following discontinuation.	IV	0.3	3 mo			X		R/NA

* Patient died of unrelated complications.
† Case described psychiatric symptoms
Abbreviations: ALT=alanine transaminase, D=days, WK=weeks, MO=months, NA=not applicable, NR=not reported, N=negative dechallenge, I=positive dechallenge; improvement, R=positive dechallenge; resolution

Reviewer's Comment: IV administration of manganese at unknown or higher than recommended doses administered over an average of 10 months (range 9 days to 4 years), mostly in patients with underlying hepatic/biliary dysfunction (n=7), have resulted in elevated manganese levels (n=9, e.g., blood and/or urine), neuropsychiatric complaints (n=9, e.g., confusion, psychomotor retardation, gait disturbance, parkinsonism, and seizures), and positive MRI findings (n=7, e.g., high-intensity signal on T1-weighted images of the globus pallidus). In patients reporting

dechallenge information (n=9), most (7 of 9) noted improvement or resolution of symptoms[i] as well as (4 of 5) improvement or resolution of MRI lesions[j] following manganese discontinuation. Notably, one study demonstrated that 60% of patients receiving long-term TPN containing an unknown manganese dose were found to have high levels of manganese, despite a lack of neurological symptoms suggesting toxicity.[38]

3.3.3 Selenium Cases (n=3)

We identified three cases of selenium toxicity from three publications in the medical literature. See Table 8 for a line listing of medical literature cases reporting selenium toxicity and associated adverse events.

Table 8. Medical Literature Cases of Selenium Toxicity*

	CITATION	AGE	SEX	DESCRIPTION	GASTROINTESTINAL	FATIGUE	ALOPECIA	PARASTHESIAS	FINGERNAIL CHANGES	CENTRAL NERVOUS SYSTEM	POSITIVE DECHALLENGE
1	Clark RF, Strukle E, Williams SR, et al. (1996) Selenium poisoning from a nutritional supplement. JAMA. 275(14): 1087-8.	36	M	DOSE: 10 tablets daily for 2 weeks (labeled as 5 mcg per tablet; FDA analysis noted 2500 to 5000 mcg per tablet, representing a 455- to 909-fold overdose) † LEVEL: Serum selenium 8.26 µmol/L (normal, 0.70 to 1.65 µmol/L)	Y	Y	Y	Y	Y		Y
2	Jensen R, Closson W, and Rothenberg R. (1984) Selenium intoxication – New York. MMWR. 33(12).	57	F	DOSE: 1 tablet daily for 77 days (labeled as 150 mcg per tablet; analysis noted 27,300 mcg per tablet, representing a 496-fold overdose)† LEVEL: 528 ng/mL	Y	Y	Y		Y		
3	Rae W, Kitley J, and Pinto A. (2018) Selenium toxicity associated with reversible leukoencephalopathy and cortical blindness. JAMA Neurology. 75(10): 1282-3.	early 50s	F	DOSE: 6-8 tablets daily for 6 months (1200-1600 mcg daily, representing a 22- to 29-fold overdose)‡ LEVEL: 5370 mcg/L (normal, 63-158 mcg/L)						Y	Y

* Known adverse events related to selenium toxicity include gastrointestinal symptoms, fatigue, alopecia, parasthesias, and fingernail changes.
† ASPEN recommends 55 mcg orally daily for adults.
‡ The patient was also taking a high-potency mineral supplement with 72 trace elements in undefined quantities

Reviewer's comment: Two articles described patients taking higher than recommended selenium supplementation doses (nearly 500- to 900-fold overdose over 2 to 11 weeks) resulting in known selenium toxicity adverse events (e.g., GI symptoms, fatigue, alopecia, fingernail changes, parasthesias); one case reported a positive dechallenge. The remaining article described a patient taking a higher than recommended selenium supplementation dose (22- to 29-fold overdose over 6 months) resulting in progressive cognitive impairment, visual loss, and

[i] Four cases described symptom improvement; three described complete resolution of symptoms.
[j] Three cases described improvement of lesions on imaging; one described complete resolution.

leukoencephalopathy that was reversible upon discontinuation. However, this case noted an unexpected absence of typical adverse events associated with selenium toxicity and noted they were unable to exclude the possibility of contaminants that may account for the adverse events described.

4 DISCUSSION

We searched the FAERS database, the CAERS database, and the medical literature and did not identify any postmarketing reports of adverse events in patients receiving intravenously administered PN solutions containing zinc sulfate, copper, manganese, or selenium within the recommended dosage range. However, we identified multiple adverse events reported with different formulations or with unknown or higher than recommended doses with copper, selenium, and manganese.

4.1.1 Copper

We identified one FAERS case that described a 2-year-old child who developed elevated transaminases following 13 months of subcutaneous cupric chloride administration. The copper dose was within the recommended dosage range for the indication of Menkes disease, however, the case lacked pertinent details such as baseline liver function.

We identified ten cases in the medical literature describing adverse events following ingestion of unknown (n=5) or higher than recommended doses (n=5, range 9- to 278-fold higher) of oral copper sulfate. The adverse events described include various gastrointestinal, hematologic, renal, hepatic, and respiratory complications as well as rhabdomyolysis, weakness/fatigue, and cardiac arrest. We also identified one case describing similar adverse events following parenteral administration of a 100-fold higher than recommended dose of copper sulfate. None of these adverse events are included in the draft labeling for TEs Injection-4; hemolysis, liver toxicity, and diarrhea are listed in the OVERDOSAGE section of the Cupric Chloride Injection label.[20] We recommend inclusion of the more informative case of parenteral administration in labeling.

We identified 14 cases in the medical literature (n=8) and FAERS database (n=6) describing systemic hypersensitivity events such as rash, pruritis, urticaria, and angioedema following insertion of a copper intrauterine device (IUD). Many cases described a positive dechallenge (n=11) and/or a positive scratch test to copper (n=7). Hypersensitivity to copper is included in the CONTRAINDICATIONS section of the draft labeling for TEs Injection-4, but not described in WARNINGS AND PRECAUTIONS or ADVERSE EVENTS.

4.1.2 Manganese

The FAERS search identified two cases of manganese toxicity with parenteral administration of manganese. One case described Parkinson-like symptoms and positive imaging following administration of TPN containing manganese at an unknown dose for an unknown duration. The second case described positive imaging following an 8000-fold overdose of manganese due to a compounding error; the patient did not display neurological symptoms despite MRI findings remaining positive for nearly 11 months.

The CAERS database search retrieved 3 cases describing neuropsychiatric adverse events (e.g., stuttering, slurring, headaches, agitation, anxiety, tremors, ataxia, sleep disruption) following ingestion of oral manganese supplementation at unknown (n=1) or 18- to 67-fold higher than recommended doses (n=2) over an average of 4.5 weeks (range 2.5 to 8 weeks).

The medical literature search identified 10 cases describing adverse events with parenteral administration of manganese at unknown (n=1) or 2.7- to 80-fold higher than recommended doses (n=9) administered over an average of 10 months (range 9 days to 4 years), of which a subset (n=7) had underlying hepatic dysfunction, biliary dysfunction, or both. The adverse events described include positive MRI findings (e.g., high-intensity signal on T1-weighted images of the globus pallidus) and neuropsychiatric complications (e.g., confusion, psychomotor retardation, gait disturbance, parkinsonism, and seizures). Notably, in patients reporting dechallenge information (n=9), most noted improvement or resolution of symptoms (7 of 9) and MRI lesions (4 of 5), following manganese discontinuation.

Neuropsychiatric adverse events and CNS deposition as well as the potential for manganese accumulation in hepatic and biliary dysfunction are not included in the draft labeling for TEs Injection-4.

4.1.3 Selenium

We identified five additional cases of adverse events related to selenium supplementation in the updated search of the medical literature (n=3) and the CAERS database (n=2). Four cases described known adverse events associated with selenium toxicity (e.g., GI symptoms, fatigue, alopecia, fingernail changes, and paresthesia) following ingestion of higher than recommended doses of oral selenium supplementation. The remaining single article described new adverse events associated with selenium toxicity such as leukoencephalopathy with progressive cognitive impairment and visual loss, reversible upon discontinuation. However, this case lacked typical adverse events associated with selenium toxicity and were unable to exclude the possibility of contaminants.

None of these adverse events are included in the draft labeling for TEs Injection-4; GI disturbances, garlic breath, fatigue, brittle nails, and myalgia are labeled in the OVERDOSE section of the Selenious Acid Injection label.[23] Adverse events previously identified in the Selenious Acid Injection review should be incorporated in the TEs Injection-4 label.

4.1.4 Zinc Sulfate

The updated FAERS, CAERS, and medical literature searches did not identify additional cases of adverse events related to zinc sulfate. Adverse events previously identified in the Zinc Sulfate review should be incorporated in the TEs Injection-4 label.

5 CONCLUSION

In conclusion, our analysis of the FAERS database, CAERS database, and medical literature did not identify any postmarketing reports of zinc sulfate, copper, manganese, or selenium-related adverse events in patients receiving intravenously administered PN solutions with these TEs

within the recommended dosage range. However, we identified multiple adverse events reported with unknown or high doses of oral and parenteral copper (e.g., GI, hepatic, renal, musculoskeletal, hematologic, respiratory, and cardiac complications); hypersensitivity events with copper; neuropsychiatric adverse events reported with unknown or high doses of parenteral manganese, many of which occurred in patients with underlying hepatic dysfunction, biliary dysfunction, or both; and known adverse events associated with selenium toxicity.

Of note, DPV-I recently (2019) completed previous postmarketing reviews for zinc sulfate and selenium. Findings included hypersensitivity events with zinc-containing products, cardiac failure with a fatal 1000-fold overdose of zinc sulfate in an infant, and mild adverse events (e.g., GI symptoms, paresthesia, alopecia, fingernail loss, signs of thyroid deficiency) with high doses of oral selenium that appeared to be reversible upon discontinuation.[k]

6 RECOMMENDATIONS

Based on this review, DPV recommends the following changes to the draft labeling for TEs Injection-4. Notably, these recommendations are not based on any fixed-dose combination products.

6.1.1 Copper

- OVERDOSAGE
  - Describe the single reported case of overdosage with parenteral copper.
- WARNINGS AND PRECAUTIONS
  - Describe the cases of hypersensitivity with copper IUDs.
- Postmarketing Experience
  - Hypersensitivity with other copper-containing products (see WARNINGS AND PRECAUTIONS).

6.1.2 Manganese

- WARNINGS AND PRECAUTIONS
  - Describe the risk of manganese accumulation with hepatic/biliary dysfunction.
  - Describe the neuropsychiatric effects and CNS deposition with manganese toxicity.
- OVERDOSAGE
  - Neuropsychiatric effects and CNS deposition with manganese toxicity (see WARNINGS AND PRECAUTIONS).
- Postmarketing Experience
  - Neuropsychiatric effects and CNS deposition with manganese toxicity (see WARNINGS AND PRECAUTIONS).

[k] The previous pharmacovigilance review also identified hypocupremia with long-term use of excess zinc. However, this should not be included in the TEs Injection label because it is a fixed-dose product that contains zinc and copper.

7 APPENDICES

7.1 APPENDIX A. PARENTERAL TRACE ELEMENT RECOMMENDATIONS AND CONCENTRATIONS (PER mL) IN AVAILABLE PRODUCTS

Trace Element	Recommended Daily Parenteral Requirements*,[39]	MTE-4 Neonatal	MTE-4 Pediatric	MTE-4	MTE-4 Concentrate	MTE-5	MTE-5 Concentrate	Individual TE	Tralement (MTE)
Chromium	Neonates: 0.05-0.3 mcg/kg (P) 0.2 mcg/kg (T) Infants and Children: 0.2 mcg/kg Adults: 10-15 mcg	0.85 mcg	1 mcg	4 mcg	10 mcg	4 mcg	10 mcg	N/A	N/A
Copper	Neonates: 29 mcg/kg (P) 20 mcg/kg (T) Infants and Children: 20 mcg/kg Adults: 300-500 mcg	100 mcg	100 mcg	400 mcg	1000 mcg	400 mcg	1000 mcg	400 mcg	300 mcg
Manganese	Neonates, Infants, and Children: 1 mcg/kg Adults: 60-100 mcg	25 mcg	25 mcg	100 mcg	500 mcg	100 mcg	500 mcg	100 mcg	55 mcg
Selenium	Neonates: 1.5-4.5 mcg/kg (P) 2 mcg/kg (T) Infants: 2-3 mcg/kg (P) 1-3 mcg/kg (T) Children: 1-3 mcg/kg Adults: 20-60 mcg	N/A	N/A	N/A	N/A	20 mcg	60 mcg	60 mcg	60 mcg
Zinc	Neonates: 0.4 mg/kg (P) 0.25 mg/kg (T) Infants: 0.45-0.5 mg/kg (P) 0.25 mg/kg (T <3 mo) 0.05 mg/kg (T >3 mo) Children: 0.05 mg/kg Adults: 2.5-5 mg	1.5 mg	1 mg	1 mg	5 mg	1 mg	5 mg	3-5 mg†	3 mg

* Recommended Daily Allowances (RDAs)[l] or Adequate Intake (AI)[m] are used to determine the recommended daily oral intake of TEs in healthy individuals.[40] Maximum daily allowances: chromium 5 mcg (infants and children), copper 500 mcg (children), manganese 500 mcg (infants and children), selenium 100 mcg (children), zinc 5 mg (infants and children).
† Zinc sulfate (NDA 209377) 10 mL vial provides 3 mg/mL of zinc, whereas the 5 mL vial provides 5 mg/mL of zinc.
Abbreviations: []=concentration, MTE=multi-trace element, N/A=not applicable, P=pre-term infant, T=term infant

[l] RDA – the average daily dietary nutrient intake level that is sufficient to meet the nutrient requirements of nearly all healthy individuals in a particular life stage and gender group.
[m] AI – the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group or groups of apparently healthy individuals that are assumed to be adequate. AI is used when an RDA cannot be determined.

7.2 APPENDIX B. SELECT SAFETY INFORMATION FROM THE APPROVED INDIVIDUAL TRACE ELEMENT PRODUCT LABELS

7.2.1 Zinc Sulfate Injection (NDA 209377)[25]

4 CONTRAINDICATIONS

Zinc sulfate Injection is contraindicated in patients with known hypersensitivity to zinc *[see Warnings and Precautions (5.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Pulmonary Embolism due to Pulmonary Vascular Precipitates

Pulmonary vascular precipitates causing pulmonary vascular emboli and pulmonary distress have been reported in patients receiving parenteral nutrition. The cause of precipitate formation has not been determined in all cases; however, in some fatal cases, pulmonary emboli occurred as a result of calcium phosphate precipitates. Precipitation has occurred following passage through an in-line filter; in vivo precipitate formation may also have occurred. If signs of pulmonary distress occur, stop the parenteral nutrition infusion and initiate a medical evaluation. In addition to inspection of the solution *[see Dosage and Administration (2.2,2.3)]*, the infusion set and catheter should also periodically be checked for precipitates.

5.2 Vein Damage and Thrombosis

Zinc Sulfate Injection has a low pH and must be prepared and used as an admixture in parenteral nutrition solutions. It is not for direct intravenous infusion.

In addition, consider the osmolarity of the final parenteral nutrition solution in determining peripheral versus central administration. Solutions with an osmolarity of 900 mOsm/L or greater must be infused through a central catheter *[see Dosage and Administration (2.1)]*. The infusion of hypertonic nutrient solutions into a peripheral vein may result in vein irritation, vein damage, and/or thrombosis. The primary complication of peripheral access is venous thrombophlebitis, which manifests as pain, erythema, tenderness or a palpable cord. Remove the catheter as soon as possible, if thrombophlebitis develops.

5.3 Aluminum Toxicity

Zinc sulfate Injection contains aluminum that may be toxic.

Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Preterm infants are particularly at risk for aluminum toxicity because the kidneys are immature, d they require large amounts of calcium and phosphate solutions, which also contain aluminum.

Patients with impaired kidney function, including preterm infants, who receive greater than 4 to 5 mcg/kg/day of parenteral aluminum can accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

Exposure to aluminum from Zinc Sulfate Injection is not more than 0.6 mcg/kg/day. When prescribing Zinc Sulfate Injection for use in parenteral nutrition containing other small volume parenteral products, the total daily patient exposure to aluminum from the admixture should be considered and maintained at no more than 5 mcg/kg/day *[see Use in Specific Populations (8.4)]*.

5.4 Monitoring and Laboratory Tests

Monitor zinc concentrations, fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, blood count and coagulation parameters throughout treatment *[see Dosage and Administration (2.4)]*.

5.5 Copper Deficiency

Several post-marketing cases have reported that high doses of supplemental zinc (approximately 10 times the recommended dosage of 3 mg/day Zinc Sulfate Injection in adults) taken over extended periods of time (i.e., months to years) may result in decreased enteral copper absorption and copper deficiency. The cases reported the following complications of copper deficiency: anemia leukopenia, thrombocytopenia, myeloneuropathy, and nephrotic-range proteinuria *[see Adverse Reactions (6)]*.

If a patient develops signs and symptoms of copper deficiency during treatment with Zinc Sulfate Injection, interrupt zinc treatment and check zinc, copper, and ceruloplasmin levels. Copper deficiency should be treated with supplemental copper administration and discontinuation of zinc supplementation.

5.6 Hypersensitivity Reactions

Hypersensitivity reactions to subcutaneously administered zinc-containing insulin products were identified in postmarketing case reports. Reported reactions included injection site induration, erythema, pruritis, papular rash, generalized urticaria, facial swelling, and dyspnea. Patients did not manifest symptoms after changing to zinc-free insulin or another insulin product with a reduced amount of zinc. In some cases, allergy testing confirmed the allergy to the zinc component of the insulin product. If hypersensitivity reactions occur, discontinue Zinc Sulfate Injection and initiate appropriate medical treatment *[see Contraindications (4)]*.

6 ADVERSE REACTIONS

No zinc-related adverse reactions have been reported in clinical studies or post-marketing reports in patients receiving intravenously administered parenteral nutrition solutions containing zinc sulfate within the recommended dosage range.

The following were identified in clinical studies or post-marketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Adverse reactions with other components of parenteral nutrition solutions:

- Pulmonary embolism due to pulmonary vascular precipitates *[see Warnings and Precautions (5.1)]*
- Vein damage and thrombosis *[see Warnings and Precautions (5.2)]*
- Aluminum toxicity *[see Warnings and Precautions (5.3)]*

Adverse reactions with the use of zinc-containing products administered by other routes of administration:

- Copper deficiency *[see Warnings and Precautions (5.5)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.6)]*

10 OVERDOSAGE

There are reported cases of overdosage with intravenous zinc in parenteral nutrition:

- Seven adult patients received an inadvertent overdosage of 50 mg to 75 mg elemental zinc per day in parenteral nutrition solution for 26 5o 60 days; 6 of the 7 patients developed hyperamylasemia (peak amylase values 557 to 1850 Klein units; normal: 130 to 310). Amylase was not reported in one patient. Serum zinc concentrations ranged from 310 to 670 mcg/dL. None of the patients developed clinical signs of pancreatitis. Five of the 7 patients died of septic complications.
- One adult patient died of infectious complications after receiving an inadvertent overdosage of 7.4 grams of zinc sulfate (equivalent to 1.2 grams of elemental zinc per day for 2.5 days) in parenteral nutrition solution over 60 hours. The serum zinc concentration was 4184 mcg/dL. Symptoms of zinc overdosage also included hyperamylasemia, thrombocytopenia, anemia, vomiting and diarrhea.

- One preterm infant born at 26 weeks gestation died of cardiac failure following a medication error in which the parenteral nutrition solution contained 330 mg/100 mL instead of 330 mcg/100 mL of zinc sulfate (overdosage of 1000-fold).

Management
There is no known antidote for acute zinc toxicity. Management of zinc overdosage is supportive care based on presenting signs and symptoms.

7.2.2 Cupric Chloride Injection (NDA 018960)[20]

CONTRAINDICATIONS

None known

WARNINGS AND PRECAUTIONS

Direct intramuscular or intravenous injection of Copper 0.4 mg/mL (Cupric Chloride Injection, USP) is contraindicated, as the acidic pH of the solution (2) may cause considerable tissue irritation.

Liver and/or biliary tract dysfunction may require omission or reduction of copper and manganese doses because these elements are primarily eliminated in the bile.

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

PRECAUTIONS

General
Administration of zinc in the absence of copper may cause a decrease in serum copper levels.

It is not recommended to administer copper to a patient with Wilson's Disease, a genetic disease of copper metabolism.

Drug interactions
Cupric ion may degrade ascorbic acid in total parenteral nutrition (TPN) solutions. In order to avoid this loss of ascorbate, multivitamin additives should be added to TPN solutions immediately prior to infusion. Alternatively, the multivitamin additive may be added to one container of TPN solution, followed by copper in a subsequent container.

Laboratory tests
Twice monthly serum assays for copper and/or ceruloplasmin are suggested for monitoring copper concentrations in long-term TPN patients. As ceruloplasmin is a cuproenzyme, ceruloplasmin assays may be depressed secondary to copper deficiency.

ADVERSE REACTIONS

None known.

OVERDOSAGE

Copper toxicity can produce prostration, behavior change, diarrhea, progressive marasmus, hypotonia, photophobia and peripheral edema. Such symptoms have been reported with a serum copper level of 286 mcg/dl. Copper toxicity can also result in hemolysis and liver toxicity, including hepatic necrosis which may be fatal. D-penicillamine has been reported effective as an antidote.

7.2.3 Manganese Sulfate Injection (NDC Code 0517-6410-25)[22]

CONTRAINDICATIONS

Manganese Sulfate Injection, USP should not be given undiluted by direct injection into a peripheral vein because of the potential for infusion phlebitis.

WARNINGS

This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

PRECAUTIONS

Manganese is eliminated via the bile. The possibility of manganese retention should be considered in patients with biliary tract obstruction. Decreasing or omitting manganese supplements entirely may be necessary for such patients. However, ancillary routes of manganese excretion include pancreatic juice, or reabsorption into the lumen of the duodenum, jejunum or ileum.

Use in Pregnancy
Safety for use in pregnancy has not been established. Use of manganese in women of childbearing potential requires that anticipated benefits be weighed against possible hazards.

ADVERSE REACTIONS

Adverse reactions to manganese at the dosage levels recommended have not been reported.

OVERDOSAGE

Manganese toxicity has not been reported in patients receiving TPN. Neither have reports of manganese toxicity from excessive intake in foods and/or beverages been published.

7.2.4 Selenious Acid Injection (NDA 209379)[23]

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pulmonary Embolism due to Pulmonary Vascular Precipitates

Pulmonary vascular precipitates causing pulmonary vascular emboli and pulmonary distress have been reported in patients receiving parenteral nutrition. The cause of precipitate formation has not been determined in all cases;

however, in some fatal cases, pulmonary emboli occurred as a result of calcium phosphate precipitates. Precipitation has occurred following passage through an in-line filter; in vivo precipitate formation may also have occurred. If signs of pulmonary distress occur, stop the parenteral nutrition infusion and initiate a medical evaluation. In addition to inspection of the solution *[see Dosage and Administration (2.2,2.3)]*, the infusion set and catheter should also periodically be checked for precipitates.

5.2 Vein Damage and Thrombosis

Selenious Acid Injection has a low pH and must be prepared and used as an admixture in parenteral nutrition solutions. It is not for direct intravenous infusion.

In addition, consider the osmolarity of the final parenteral nutrition solution in determining peripheral versus central administration. Solutions with an osmolarity of 900 mOsm/L or greater must be infused through a central catheter *[see Dosage and Administration (2.1)]*. The infusion of hypertonic nutrient solutions into a peripheral vein may result in vein irritation, vein damage, and/or thrombosis. The primary complication of peripheral access is venous thrombophlebitis, which manifests as pain, erythema, tenderness or a palpable cord. Remove the catheter as soon as possible, if thrombophlebitis develops.

5.3 Aluminum Toxicity

Selenious Acid Injection contains aluminum that may be toxic.

Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Preterm infants are particularly at risk for aluminum toxicity because the kidneys are immature, d they require large amounts of calcium and phosphate solutions, which also contain aluminum.

Patients with impaired kidney function, including preterm infants, who receive greater than 4 to 5 mcg/kg/day of parenteral aluminum can accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

Exposure to aluminum from Selenious Acid Injection is not more than 0.6 mcg/kg/day. When prescribing Selenious Acid Injection for use in parenteral nutrition containing other small volume parenteral products, the total daily patient exposure to aluminum from the admixture should be considered and maintained at no more than 5 mcg/kg/day *[see Use in Specific Populations (8.4)]*.

5.4 Monitoring and Laboratory Tests

Monitor selenium concentrations, fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, blood count and coagulation parameters throughout treatment *[see Dosage and Administration (2.5)]*.

6 ADVERSE REACTIONS

No selenium-related adverse reactions have been reported in clinical studies or post-marketing reports in patients receiving intravenously administered PN solutions containing selenious acid within the recommended dosage range.

The following adverse reactions associated with use of other components of PN solutions were identified in clinical studies or post-marketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- Pulmonary embolism due to pulmonary vascular precipitates *[see Warnings and Precautions (5.1)]*
- Vein damage and thrombosis *[see Warnings and Precautions (5.2)]*
- Aluminum toxicity *[see Warnings and Precautions (5.3)]*

10 OVERDOSAGE

There are no known cases of overdosage with intravenous selenious acid in parenteral nutrition.

Overdosage has been reported with oral selenium. Available selenium concentrations in these subjects have been reported using various assays and laboratory-based reference ranges over a period of time. Interpret results in the context of current reported ranges.

For oral selenium, the Tolerable Upper Limit (UL) is 400 mcg/day and the No Observed Adverse Effect Level (NOAEL) is 800 mcg/day. The estimated oral bioavailability of selenium is approximately 70%.

Acute Oral Toxicity Effects

Serious adverse events and deaths have been reported with acute oral toxicity, however, there is no clear correlation between the amount ingested, signs and symptoms of toxicity, or selenium blood concentrations.

With severe toxicity, the most common presenting symptoms within a few hours post-ingestion of oral doses greater than 1 gram/day of selenium are gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), altered mental status, and "garlic" breath odor.

Death from circulatory collapse has been reported after oral ingestion of 5 to 10 grams of selenium. Selenium serum or blood concentrations in fatal cases have been reported in the range of 190 mcg/dL to 3800 mcg/dL.

Mild to moderate intoxication (myalgia, muscle spasms, and irritability) has been reported in patients with selenium serum or blood concentrations in the range of 41 to 750 mcg/dL.

Chronic Selenosis

Chronic daily exposure to selenium from dietary sources (0.003 to 0.007 grams/day) or oral supplements (0.0016 to 0.25 grams/day) may result in alopecia and nail brittleness. Other signs include gastrointestinal disturbances, skin rash, garlic breath, fatigue, irritability and nervous system abnormalities including paresthesia and ataxia.

Selenium serum or blood concentrations in patients in China exposed through oral (non-dietary) supplementation were in the range of 32 to 150 mcg/dL.

Management
There is no known antidote for acute selenium toxicity. Management of selenium overdosage is supportive care based on presenting signs and symptoms.

7.3 APPENDIX C. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

CFSAN Adverse Event Reporting System (CAERS)

CAERS captures any adverse events or complaints related to foods, dietary supplements, or cosmetics. These can include minor to major medical events, but also complaints about off-taste or color of a product, defective packaging, and other non-medical issues. Healthcare professionals and consumers may report adverse events directly to the FDA or to the products' manufacturers. If a manufacturer receives a serious adverse event report related to a dietary supplement, the manufacturer is required to send the report to FDA as specified by law. The reports received voluntarily by consumers, health professionals, and manufacturers, and the mandatory reports from dietary supplement manufacturers are entered into CAERS.

CAERS data have limitations. The adverse event reports about a product and the total number of adverse event reports for that product in CAERS only reflect information *as reported* and do not represent any conclusion by FDA about whether the product actually caused the adverse events. The reports submitted to FDA vary in the quality and reliability of the information provided. Some reports to FDA do not necessarily include all relevant data, such as whether an individual also suffered from other medical conditions or used other products or medications at the same time. Reports may not include accurate or complete contact information for FDA to seek further information about the event, or complainants may choose not to participate in a follow-up investigation. When important information is missing from a report, it is difficult for FDA to fully evaluate whether the product caused the adverse event or simply coincided with it.

7.4 APPENDIX D. FAERS LINE LISTING OF CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	8/6/1991	4815923	1		Direct	2	Male	USA	OT
2	6/1/2016	12424592	3	US-PFIZER INC-2016274397	Expedited (15-Day)	52	Female	USA	HO, OT
3	4/11/2008	6612496	2	DE-BRISTOL-MYERS SQUIBB COMPANY-14143895	Expedited (15-Day)	12	Female	Germany	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: HO=Hospitalization, OT=Other Medically Significant

7.5 APPENDIX E. LINE LISTING OF REPORTS RETRIEVED BY CAERS DATABASE

	Date Created	PRIMO ID #	Type of Report	Age (years)	Sex	Product(s)	Country Derived	Serious Outcome(s)
Manganese Cases								
1	9/26/2013	170513	VOLUNTARY	47	F	MANGANESE ASPORATATE	USA	HO, RI, DS
2	5/15/2019	2019-CFS-004830*	VOLUNTARY	52	F	DOUGLAS LABORATORIES CHELATED MANGANESE	USA	DS
3	9/19/2019	2019-CFS-009622	VOLUNTARY	56	F	STANDARD PROCESS MANGANESE B12	USA	OT
Selenium Cases								
4	9/30/2019	2019-CFS-009973	VOLUNTARY	9	F	PURE ENCAPSULATIONS SELENIUM	USA	NR
5	9/30/2019	2019-CFS-009971*	VOLUNTARY	39	F	PURE ENCAPSULATIONS SELENIUM	USA	NR
Zinc Cases								
6	5/28/2019	2019-CFS-005255	MANDATORY	56	M	PURITAN'S PRIDE ZINC (ZINC GLUCONATE)	USA	OT

* Duplicate reports: PRIMO ID# 2019-CFS-004830 and 2019-CFS-002120, PRIMO ID# 2019-CFS-009971 and 2019-CFS-010031

† As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case may have more than one serious outcome.

Abbreviations: HO=Hospitalization, DS= Disability, OT=Other medically significant, RI=Required intervention, NR=not reported

7.6 APPENDIX F. MEDICAL LITERATURE CASES OF COPPER TOXICITY WITH ORAL INGESTION AND ASSOCIATED ADVERSE EVENTS

	CITATION	AGE	SEX	ROUTE	DOSING (g)	DURATION	GASTROINTESTINAL	HEPATIC	RENAL	WEAKNESS/FATIGUE	RHABDOMYOLYSIS	INTRAVASCULAR HEMOLYSIS	RESPIRATORY	CARDIAC
1	Cho Y.S., Moon J.M., Jeong Y.H., Lee D.H., Chun B.J. (2018) Successful extracorporeal life support in respiratory failure after copper sulphate ingestion. National Medical Journal of India. 31(2): 83-85.	44	F	Oral	NR	Once						X	X	
2	Lubica C, Rudolf M, Jiri L. (2017) Acute copper sulfate poisoning. Journal of the College of Physicians and Surgeons Pakistan. 27(8): 527-8.	53	M	Oral	120	Once	X*	X	X	X	X	†		
3	Gamakaranage, C.S., Rodrigo, C., Weerasinghe, S. et al. (2011) Complications and management of acute copper sulphate poisoning; a case discussion. J Occup Med Toxicol 6,34.	26	M	Oral	30	Once	X	X	X			X		
4	Gamakaranage, C.S., Rodrigo, C., Weerasinghe, S. et al. (2011) Complications and management of acute copper sulphate poisoning; a case discussion. J Occup Med Toxicol 6,34.	45	M	Oral	50	Once	X		X	X		X		
5	Valsami S, Stamoulis K, Lydataki E, and Fountoulaki-Paparizos L. (2011) Acute copper sulphate poisoning: a forgotten cause of severe intravascular haemolysis. Britash Journal of Haematology. 156(3): 294.	25	M	Oral	NR	Once	X	X	X		X	X		
6	Hassan S, Shaikh MU, Ali N, and Riaz M. (2010) Copper sulphate toxicity in a young male complicated by methemoglobinemia, rhabdomyolysis and renal failure. Journal of the College of Physicians and Surgeons Pakistan. 20(7): 490-491.	22	M	Oral	NR	Once	X	X	X		X	†	X	
7	Faure A, Mathon L, Poupelin JC, Allaouchiche B, and Chassard D. (2003) Acute cupric sulfate intoxication: Pathophysiology and therapy about a case report. Annales Francaises d'Anesthesie et de Reanimation. 22(6): 557-559.	38	NR	Oral	NR	Once	X					X		
8	Takeda T., Yukioka T., Shimazaki S. (2000) Cupric sulfate intoxication with rhabdomyolysis, treated with chelating agents and blood purification. Internal Medicine. 39(3): 253-255.	18	M	Oral	8	Once	X		X	X	X	X		
9	Gulliver JM. (1991) A fatal copper sulfate poisoning. Journal of Analytical Toxicology. 15: 341-2.	11	F	Oral	NR	Once								X
10	Jantseh W, Kulig K, and Rumack BH. (1984) Massive copper sulfate ingestion resulting in hepatotoxicity. Journal of Toxicology: Clinical Toxicology. 22(6): 585-588.	42	M	Oral	250	Once	X	X			X			

* Case also noted mild pancreatitis.
† Case noted methemoglobinemia.
Abbreviations: IV=intravenous, subQ=subcutaneous, NR=not reported

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 18, 2020
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 209376
Product Name, Dosage Form, and Strength:	Tralement (trace elements injection 4*, USP [*contains: zinc, copper, manganese, and selenium]) injection, 3 mg, 0.3 mg, 55 mcg, and 60 mcg per mL
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	American Regent, Inc
FDA Received Date:	September 3, 2019 and October 22, 2019
OSE RCM #:	2019-1889
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader (Acting):	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the approval process for Tralement (trace elements injection 4*, USP [*contains: zinc, copper, manganese, and selenium]) injection, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the proposed Tralement prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

American Regent submitted an NDA for Tralement (trace elements injection 4*, USP [*contains: zinc, copper, manganese, and selenium]) injection. We reviewed the prescribing information, carton labeling, and container label. We identified areas in the Tralement container label and carton labeling that can be improved to increase readability and prominence of important information.

We note that Office of Pharmaceutical Quality provided the following information via email dated March 3, 2020, for the recommended established name and strength as a result of a CDER PQLC meeting (January 31, 2020) for this NDA.

> Trace Elements Injection 4*, USP
>
> *Each mL provides: zinc 3 mg, copper 0.3 mg, manganese 55 mcg, selenium 60 mcg

On the side panel (if space is permitted), to include the following:

> Each mL contains: zinc sulfate 7.41 mg, cupric sulfate 0.75 mg, manganese sulfate 151 mcg, selenious acid 98 mcg

4 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Applicant.

4.1 RECOMMENDATIONS FOR AMERICAN REGENT, INC

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Tray Labeling)

1. Revise the established name to read: Trace Elements Injection 4*, USP
2. Add the strength statement below the established name: * Each mL provides: zinc 3 mg, copper 0.3 mg, manganese 55 mcg, selenium 60 mcg
3. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
4. Revise the side panel to read: Each mL contains: zinc sulfate 7.41 mg, cupric sulfate 0.75 mg, manganese sulfate 151 mcg, selenious acid 98 mcg
5. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Tray Labeling

1. To ensure consistency with the Prescribing Information, revise the statement, "(b) (4)" to read "Recommended Dosage: See prescribing information."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tralement received on October 22, 2019 from American Regent, Inc.

Table 2. Relevant Product Information for Tralement	
Initial Approval Date	N/A
Active Ingredient	trace elements injection 4*, USP [*contains: zinc, copper, manganese, and selenium]
Indication	(b) (4) as a source of zinc, copper, selenium, and manganese for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated
Route of Administration	Intravenous injection
Dosage Form	injection
Strength	3 mg, 0.3 mg, 55 mcg, and 60 mcg
Dose and Frequency	(b) (4)
How Supplied	Supplied as 1 mL pharmacy bulk package vials, (b) (4) vials packaged in trays of 25 vials per tray
Storage	Store at 20° to 25°C (68° to 77°F), excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]

APPENDIX B. PREVIOUS DMEPA REVIEWS – N/A
APPENDIX C. HUMAN FACTORS STUDY – N/A
APPENDIX D. ISMP NEWSLETTERS – N/A
APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A
APPENDIX F. N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Tralement labels and labeling submitted by American Regent, Inc.

- Container label received on September 3, 2019
- Carton labeling received on September 3, 2019
- Prescribing Information (Image not shown) received on October 22, 2019, available from \\CDSESUB1\evsprod\NDA209376\209376.enx

G.2 Label and Labeling Images

Vial label

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
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Division of Pediatric and Maternal Health Review

Date: January 30, 2020 **Date consulted:** September 12, 2019

From: Carrie Ceresa, Pharm D., MPH, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: The Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: TRALEMENT (Trace Element Injection-4, USP; zinc sulfate 3000 mcg, cupric sulfate 300 mcg, selenious acid 60 mcg and manganese sulfate 55 mcg) for intravenous use

NDA: 209376

Applicant: American Regent, Inc.

Subject: Pregnancy and Lactation Labeling Formatting Recommendations

Proposed Indication: for adult and pediatric patients as a source of zinc, copper, selenium, and manganese for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

Materials Reviewed:

- September 9, 2019, NDA 209376, New Drug Application (NDA) 505(b)(2) for TRALEMENT (trace element injection-4) intravenous injection

- February 6, 2019, DPMH review for selenious acid injection, NDA 209379, Carrie Ceresa, Pharm D., MPH., Clinical Analyst, DARRTS Reference ID 4385634[1]
- April 2, 2019, DPMH review for zinc sulfate injection, NDA 209377, Kristie Baisden, DO, Medical Officer, DARRTS Reference ID 4412101[2]

Consult Question: "Assistance in review of proposed NDA labeling and PLLR (Pregnancy and Lactation Labeling Rule) labels."

INTRODUCTION AND BACKGROUND

Regulatory History

On September 5, 2019, American Regent, Inc., submitted NDA 209376 which is a 505(b)(2) application for TRALEMENT (Trace Element Injection-4, USP; zinc sulfate 3000 mcg, cupric sulfate 300 mcg, selenious acid 60 mcg and manganese sulfate 55 mcg) for intravenous use. The product indication is for adult and pediatric patients as a source of zinc, copper, selenium, and manganese for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. The applicant is relying on published literature for the approval of this 505(b)(2) application. The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) on September 12, 2019, to assist with the Pregnancy and Lactation subsections of labeling.

Table 1: TRALEMENT Drug Characteristics[3]

(The reader is referred to the two previous DPMH, maternal health consult reviews for drug characteristic information for selenious acid completed on February 6, 2019[4] and zinc sulfate completed on April 2, 2019.[5])

Dose and Administration	Not for direct intravenous administration; is supplied as a preservative free 1 mL single-dose vial for admixing and transfer to parenteral nutrition container
Warnings and Precautions	Pulmonary embolism due to pulmonary vascular precipitates; vein damage and thrombosis; aluminum toxicity; monitoring and lab tests of electrolyte status; (b) (4); hypersensitivity reactions
Adverse Reactions	(b) (4)

[1] The DPMH review for selenious acid injection was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

[2] The DPMH review for zinc sulfate injection was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

[3] Applicant's Proposed TRALEMENT Product Insert.

[4] February 6, 2019, DPMH review for selenious acid injection, NDA 209379, Carrie Ceresa, Pharm D., MPH., Clinical Analyst, DARRTS Reference ID 4385634.

[5] April 2, 2019, DPMH review for zinc sulfate injection, NDA 209377, Kristie Baisden, DO, Medical Officer, DARRTS Reference ID 4412101.

Practice Guidelines for Parenteral Nutrition in Pregnancy[5,6]
Few pregnant women will require use of parental nutrition; however, the American College of Obstetrics and Gynecology (ACOG) supports the use of parental nutrition when both anti-emetic medications and enteral feedings via naso-gastric tube have failed to maintain the pregnant women's weight in patients with patients with hyperemesis gravidarum.

Reviewer comment: DPMH previously reviewed published literature related to malnutrition in pregnancy.[4,5] DPMH concluded that severe malnutrition in pregnancy is associated with adverse maternal and fetal outcomes including preterm birth, low birth weight, intrauterine growth restriction, congenital malformations and perinatal mortality. Therefore, DPMH recommends subsection 8.1 of labeling for this product include a Clinical Considerations informing prescribers of these risks.

REVIEW

Nonclinical Experience
Animal reproduction studies have not been conducted with TRALEMENT injection.

Review of Literature
Applicant's Review of Literature
The applicant conducted a review of published literature. With regard to zinc and selenium exposure during pregnancy the applicant refers to the approvals of NDA 209377 and 209379. For copper and manganese, the reader is referred to the applicant's submission for search parameters. According to the applicant, their search did not reveal any informative publications on the exposure of copper and manganese during pregnancy. The applicant does state however that according to the Institute of Medicine (IOM) that estimates of requirements of management in pregnant women is extrapolated from daily dietary requirements.

DPMH's Review of Literature
DPMH conducted a search of published literature using PubMed and Embase regarding the components of TRALEMENT exposure during pregnancy using the following search terms, "zinc sulfate, cupric sulfate, selenious acid and manganese sulfate and fetal malformations," "zinc sulfate, cupric sulfate, selenious acid and manganese sulfate and spontaneous abortion and miscarriage," "zinc sulfate, cupric sulfate, selenious acid and manganese sulfate and embryo-fetotoxicity."

The reader is referred to the two previous DPMH, maternal health consult reviews for published literature with regard to zinc sulfate and selenious acid exposure during pregnancy.[4,5] No additional relevant literature was found for review.

No additional information was found for review in Micromedex or *Drugs in Pregnancy and Lactation* by Briggs and Freeman.

[6] ACOG Practice Bulletin Clinical Management Guidelines for Ob/Gyns, No. 189. Nausea and Vomiting of Pregnancy, January 2018.

Reviewer comment: The applicant addressed the PLLR requirements. There are limited published data on the effects of each of the trace elements included in TRALEMENT. Each of the trace elements has been used over decades as part of parenteral nutrition, not necessarily for replacement or deficiency, but as a source of trace elements for women who are unable to take these trace elements orally. Published literature does not provide a clear association of adverse pregnancy outcomes with intake of these trace elements. In addition, according to published literature severe malnutrition may lead to adverse pregnancy outcomes. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

LACTATION

Nonclinical Experience

Animal lactation studies have not been conducted with TRALEMENT injection.

Review of Literature

Applicant's Review of Literature

The applicant conducted a review of published literature. With regard to zinc and selenium exposure during lactation, the applicant refers to the approvals of NDA 209377 and 209379. For copper and manganese, the reader is referred to the applicant's submission for search parameters. According to the applicant their search did not reveal any informative publications on the exposure of copper and manganese during lactation. The applicant does state however that according to the Institute of Medicine (IOM) that estimates of requirements of management in lactating women is extrapolated from daily dietary requirements.

DPMH's Review of Literature

DPMH conducted a search of published literature using PubMed and Embase regarding the components of TRALEMENT exposure during lactation using the following search terms, "zinc sulfate, cupric sulfate, selenious acid and manganese sulfate and lactation." The relevant data are summarized below. No additional data were found in LactMed[7] or *Drugs in Pregnancy and Lactation* by Briggs and Freeman.[8] Also, The reader is referred to the two previous DPMH, maternal health consult reviews for information with regard to zinc sulfate and selenious acid exposure during lactation.[4,5]

Published Literature

Copper and Zinc

Yalcin S et al., (2015),[9] conducted a study in Turkey to evaluate zinc and copper concentrations in breast milk. Samples of human milk were collected postpartum at week 2, month 2, 4 and 9.

[7] http://toxnet.nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[8] Briggs, GG and Freeman, R., Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk Online version: http://ovidsp.tx.ovid.com/sp-3.31.1b/ovidweb.cgi.

[9] Yalcin S et al., 2015, Zinc and Copper Concentrations in Breast Milk During the First Nine Months of Lactation: A Longitudinal Study. Pediatrics, Official Journal of the American Academy of Pediatrics, www.aappublications.org/news, S14.

The mean concentrations of Zn and Cu (n=172) were 4.84 6 2.24 mg/L and 452 6 129 mg/L, respectively, at week 2. A reduction was observed in both elements over time as lactation continued and maternal anemia and iron supplementation appeared to influence the amount of zinc and copper in samples.

Copper, zinc and manganese
Klein L et al., (2017),[10] conducted a study to characterize essential nutrients and toxic metals in human milk using milk samples from lactating women (n=70) in Argentina (n= 21), Namibia (n=6), Poland (n=23) and the United States (n=20). Milk concentrations of calcium, zinc, iron, copper, manganese, lead, arsenic and cadmium were measured using coupled plasma mass spectrometry. The differences in levels of calcium and manganese showed more differences across the populations which is most likely due to differences in diet and environmental exposure. All elements were present in human milk. The overall aim of the study was to conclude whether trace metal concentrations in diverse populations were different. The authors concluded that due to environmental contamination of samples they were prevented from drawing definitive conclusions.

Medication and Mothers Milk[11]
There are no data on manganese sulfate or cupric sulfate in *Medication and Mothers Milk;* however, the following information is available regarding selenium and zinc:

Selenium
"Selenium is an essential trace element which is needed for antioxidant enzymes. Selenium is often found in the form of various selenoproteins and is involved in various biochemical and physiological including the enhancement of immunity and oxidation resistance. Blood Selenium concentrations generally increase from birth until the age of 6 months in breastfed infants and then remain stable in the long term. Recommended dietary allowance of selenium for breastfeeding women is 70 µg/day. Foods that are rich in selenium includes tuna, brazil nuts, beef, cod, chicken, turkey, egg, cheese, rice, oatmeal, bread, and walnut. Interestingly, formula levels are often deficient in this important trace element."

Zinc salts
"Zinc is an essential element that is required for enzymatic function within the cell. Zinc deficiencies have been documented in newborns and premature infants with symptoms such as anorexia nervosa, arthritis, diarrhea, eczema, recurrent infections, and recalcitrant skin problems. The Recommended Daily Allowance (RDA) for adults is 12-15 mg/day. The average oral dose of supplements is 25-50 mg/day; higher doses may lead to gastritis... Supplementation with 25-50 mg/day is probably safe, but excessive doses are discouraged. Another author has shown that zinc levels in breastmilk are independent of maternal plasma zinc concentrations or dietary zinc intake."

[10] Klein L et al., (2017), Concentrations of trace elements in human milk: Comparisons among women in Argentina, Namibia, Poland and the United States. Public Library of Science (PLoS ONE), 12(8): e0183367.
[11] Hale, Thomas. Medications and Mother's Milk. www.halesmeds.com. accessed 6 January 2020.

Reviewer comment: The applicant addressed the PLLR requirements. The amounts of manganese, zinc, selenious acid and cupric acid exposure through TPN are expected to fall within levels that are considered adequate for daily intake. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Animal reproduction studies have not been conducted with TRALEMENT injection.

Review of Literature

The applicant conducted a review of published literature, and no data were found.

DPMH conducted a review of available published literature on zinc sulfate, cupric sulfate, selenious acid and manganese sulfate exposure and effects on fertility. The reader is referred to the two previous DPMH, maternal health consult reviews with regard to zinc sulfate and selenious acid exposure and effects on fertility.[4,5] No additional relevant literature was found for review.

Reviewer comment: The applicant addressed the PLLR requirements. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

Animal reproduction studies have not been conducted. There are limited published data on the effects of each of the trace elements included in TRALEMENT on pregnancy. Each of the trace elements has been used over decades as part of parenteral nutrition in pregnant women, not necessarily for replacement or deficiency, but as a source of trace elements for women who are unable to take these trace elements orally. Published literature do not provide a clear association of adverse pregnancy outcomes with use of these trace elements. The amounts of manganese, zinc, selenious acid and cupric acid exposure through TPN are expected to fall within levels that are considered adequate for daily intake. In addition, according to published literature, severe malnutrition may lead to maternal and fetal outcomes including preterm birth, low birth weight, intrauterine growth restriction, congenital malformations and perinatal mortality, and the American College of Obstetrics and Gynecology (ACOG) supports the use of parental nutrition when both anti-emetic medications and enteral feedings via naso-gastric tube have failed to maintain the pregnant women's weight in patients with patients with hyperemesis gravidarum. DPMH agrees with this recommendation.

Lactation

DPMH recommends subsection 8.2 of labeling state that all 4 elements (zinc sulfate, cupric sulfate, selenious acid and manganese sulfate) are present in human milk. The amounts of manganese, zinc, selenious acid and cupric acid exposure through TPN are expected to fall within levels that are considered adequate for daily intake. No adverse events have been reported in breastfed infants after maternal administration of zinc sulfate, cupric sulfate,

selenious acid and manganese sulfate at recommended doses in parenteral nutrition. Administration of the approved recommended doses of zinc sulfate, cupric sulfate, selenious acid and manganese sulfate in parenteral nutrition is not expected to cause harm to a breastfed infant. DPMH recommends the inclusion of the following risk/benefit statement, "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRALMENT and any potential adverse effects on the breastfed infant from TRALENT or from the underlying maternal condition.

Females and Males of Reproductive Potential

DPMH recommends subsection 8.3 of labeling be omitted. There are no data on the effects of cupric acid or manganese sulfate on fertility. Limited available human data suggest zinc sulfate does not adversely affect fertility. Limited data reviewed in a previous review by DPMH suggest that selenium may cause effects on fertility by improving pregnancy outcomes in selenium deficient women at risk for pre-eclampsia but the data are conflicting. The reader is referred to the two previous DPMH reviews on selenious acid and zinc sulfate. Pregnancy testing and contraception subheadings are not recommended because there are no data to suggest zinc sulfate, cupric sulfate, selenious acid or manganese sulfate are associated with embryo-fetal toxicity.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Administration of the recommended dose of TRALEMENT in parenteral nutrition as a source of zinc, copper, selenium and manganese for parenteral nutrition when oral intake is not possible is not expected to cause major birth defects, miscarriage, or adverse maternal or fetal outcomes. Deficiency of trace elements may result in adverse pregnancy and fetal outcomes *(see Clinical Considerations).* Animal reproduction studies have not been conducted with TRALEMENT.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. n the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo-Fetal Risk

Deficiency of trace elements, including zinc sulfate, cupric sulfate, selenious acid and manganese sulfate, is associated with adverse pregnancy and fetal outcomes. Pregnant women have an increased metabolic demand for trace elements. Parenteral nutrition with TRALEMENT should be considered if a pregnant woman's nutritional requirements cannot be fulfilled by oral or enteral intake.

8.2 Lactation

Risk Summary

Zinc sulfate, cupric sulfate, selenious acid and manganese sulfate are present in human milk. Administration of the approved recommended dose of these trace elements in parenteral nutrition is not expected to cause harm to a breastfed infant. There is no information on the effects of these trace elements on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRALEMENT and any potential adverse effects on the breastfed infant from TRALEMENT or from the underlying maternal condition.

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/s/

CARRIE M CERESA
01/30/2020 12:39:18 PM

MIRIAM C DINATALE
01/31/2020 09:33:38 AM

LYNNE P YAO
02/06/2020 09:26:43 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology Literature Review

Date:	January 28, 2020
Reviewer:	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Team Leader:	Catherine Callahan, PhD MA Division of Epidemiology I
Deputy Director:	CAPT. Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Drug Name:	Trace Elements Injection-4 (Tralement™)
Subject:	Medical literature supporting parenteral nutrition guidelines for manganese dosing
Application Type/Number:	NDA 209376
Applicant/sponsor:	American Regent (formerly Luitpold Pharmaceuticals)
OSE RCM #:	2019-1925

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EXECUTIVE SUMMARY

Responding to a request from the Division of Gastroenterology and Inborn Error Products (DGIEP), the Division of Epidemiology I (DEPI) identified study reports in medical literature that might support a dosing recommendation for manganese (Mn) in parenteral nutrition (PN).

The request from DGIEP concerns Trace Elements Injection-4 (NDA 209376), a trace-element PN additive containing selenium (as selenious acid), zinc (as zinc sulfate heptahydrate), copper (as cupric sulfate), and manganese (as manganese sulfate monohydrate).

DEPI used a systematic approach to identify six study reports in medical literature that DGIEP might consider as evidence that supports a dosing recommendation for Mn in PN.

1 INTRODUCTION

Responding to a request from the Division of Gastroenterology and Inborn Error Products (DGIEP), the Division of Epidemiology I (DEPI) identifies study reports in medical literature that might support a dosing recommendation for manganese (Mn) in parenteral nutrition (PN).

The request from DGIEP concerns Trace Elements Injection-4 (NDA 209376), a trace-element PN additive containing selenium (as selenious acid), zinc (as zinc sulfate heptahydrate), copper (as cupric sulfate), and manganese (as manganese sulfate monohydrate).

The Sponsor seeks approval for Trace Elements Injection-4 through a 505(b)(2) literature-only pathway. To identify relevant literature, the Sponsor commissioned a systematic literature review, conducted by [redacted] (b) (4) DEPI previously validated the [redacted] (b) (4) search in reviews completed for Selenious Acid Injection (NDA 209379) and Zinc Sulfate Injection (NDA 209377).[1]

On September 16, 2019, DGIEP requested "DEPI consultation on the methodology and approach in literature submitted to support the efficacy and safety of Selenious Acid, Zinc Sulfate, Copper and Manganese."[2] During a meeting on November 13, 2019, DGIEP agreed to limit this request to cover study reports in medical literature that might support recommendations in FDA labels for copper and manganese in parenteral nutrition (PN) with respect to optimal dosing for efficacy

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[1] Weissfeld JL, Bright PL, Sandhu SK. Evaluation of a Systematic Review of Medical Literature: Selenious Acid for Parenteral Nutrition, filed under NDA 209379 on March 12, 2019 (DARRTS Reference ID: 4402464).

Weissfeld JL, Bright PL, Sandhu SK. Evaluation of a Systematic Review of Medical Literature: Zinc Sulfate for Parenteral Nutrition, filed under NDA 209377 on April 30, 2019 (DARRTS Reference ID: 4426323).

[2] Request for Consultation filed under NDA 209376 on September 16, 2019 (DARRTS Reference ID: 4492272).

and safety. DEPI filed a separate report for copper previously.[3,4]

2 REVIEW METHODS AND MATERIALS

2.1 Documents reviewed

Reference	Date	Title
(b) (4) Report - Adults	2016-JUN-10	Systematic Literature Review for Trace Elements in Parenteral Nutrition: Manganese in the Adult Population, submitted to NDA 209377 (eCTD 0002) on October 22, 2018.
(b) (4) Report - Pediatric	2016-JUN-10	Systematic Literature Review for Trace Elements in Parenteral Nutrition: Manganese in the Pediatric Population, submitted to NDA 209377 (eCTD 0002) on October 22, 2018.
Clinical Overview - Adult	2017-OCT-14	Clinical Overview for Trace Element Injection (Adult), submitted to NDA 209376 (eCTD 0003) on October 12, 2018.
Clinical Overview - Pediatric	2017-OCT-14	Clinical Overview for Trace Element Injection (Pediatric), submitted to NDA 209376 (eCTD 0003) on October 12, 2018.
SCE - Adult	2017-OCT-14	Summary of Clinical Efficacy for Trace Element Injection (Adult), submitted to NDA 209376 (eCTD 0003) on October 12, 2018
SCE - Pediatric	2017-OCT-14	Summary of Clinical Efficacy for Trace Element Injection (Pediatric), submitted to NDA 209376 (eCTD 0003) on October 12, 2018.
SCS - Adult	2017-OCT-14	Summary of Clinical Safety for Trace Element Injection (Adult), submitted to NDA 209376 (eCTD 0003) on October 12, 2018.
SCS - Pediatric	2017-OCT-14	Summary of Clinical Safety for Trace Element Injection (Pediatric), submitted to NDA 209376 (eCTD 0003) on October 12, 2018.
Draft Label	2019-SEP-04	Prescribing Information for TRALEMENT™ (Trace

[3] Weissfeld JL, Callahan C, Sandhu SK. Medical literature supporting parenteral nutrition guidelines for copper dosing, filed under NDA 209376 on December 23, 2019 (DARRTS Reference ID: 4538531).

[4] For reviews completed by FDA to establish selenium and zinc PN dosing, see

UniReview: A Multi-Disciplinary Review and Evaluation for Selenious Acid, filed under NDA 209379 on March 2, 2019 (DARRTS Reference ID: 4427655).

UniReview: A Multi-Disciplinary Review and Evaluation for Selenious Acid, filed under NDA 209377 on July 18, 2019 (DARRTS Reference ID: 4464465).

Reference	Date	Title
		Elements Injection-4), submitted to NDA 209376 (eCTD 0012) on September 5, 2019.
Clinical Information Amendment	2019-DEC-06	Clinical Information Amendment - Response to 74-Day Letter: No Filing Review Issues Identified, submitted to NDA 209376 (eCTD 0017) on December 6, 2019.

2.2 Review methods

DEPI identified source literature about Mn dosing for PN by examining articles (1) identified by (b) (4) systematic literature search, (2) discussed by the Sponsor in documents submitted to NDA 209376, (3) referenced in guideline statements or review articles, and (4) identified by independent PubMed search (**APPENDIX 1**).

3 REVIEW RESULTS

3.1 Professional guidelines for dosing manganese in parenteral nutrition

Early guidelines permitted adult dosing with Mn as high as 800 mcg/day [1,2]. A current guideline identifies 55 mcg/day in adults and 1 mcg/kg/day (55 mcg/day maximum) in neonates and children as appropriate PN dosing for Mn.[5] This guideline presumes that the typical adult PN formulation provides <40 mcg Mn/day as contaminants [3,4].

Age-specific dietary reference ranges for adequate Mn intake (*e.g.*, 1.8 and 2.3 mg/day in adult women and men, respectively),[6] combined with knowledge about intestinal bioavailability (<5%) [5], indicate the Mn dose (*e.g.*, ≈100 mcg/day in adults) possibly required for PN.

Recent guidelines (1988 and later; [3-12]) uniformly present 100 mcg/day in adults and 1 mcg/kg/day in children as the highest Mn dose appropriate for routine PN. Concern about neurotoxicity from excess Mn supplementation motivates these limits on Mn dosing. Evidence in medical literature for excess Mn supplementation include:

- Studies showing high blood Mn concentrations and intense basal ganglia on T1-weighted magnetic resonance images (MRIs) in adult [13-21] and pediatric [22-25] patients on PN.
- Case reports of Parkinsonian-like symptoms in patients on Mn-supplemented PN [26-30].

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[5] ASPEN, Appropriate Dosing for Parenteral Nutrition: ASPEN Recommendations. January 2019, Accessed at http://www.nutritioncare.org/PNDosing on January 10, 2020.

[6] Institute of Medicine, 2006, Dietary Reference Intakes for Manganese by Life Stage Group, accessed at https://www.nap.edu/read/11537/chapter/39 on January 10, 2020.

3.2 Manganese dosing recommended in draft label for Trace Elements Injection-4

Each mL of Trace Elements Injection-4 contains 55 mcg manganese (Mn) as manganese sulfate. For patients on parenteral nutrition (PN), the draft label for Trace Elements Injection-4 recommends dosing [redacted (b) (4)] [7] These recommendations correspond to Mn dosing in adults and heavier children at 55 mcg/day and lighter children at [redacted (b) (4)] mcg/day.

[redacted (b) (4)]

3.3 Empirical support for Mn dosing at 55 mcg/day in adults

DEPI assessed 72 articles for information about Mn dosing in adults (**APPENDIX 3**). DEPI found reports from three clinical studies that dosed adult PN patients at 55 mcg Mn/day (1 µmol/day).

- **Takagi 2002** [31] conducted (in Japan between May 1994 and March 1999) a Mn dose-finding study in 12 adults (50% men; mean age 43.5 years) on home parenteral nutrition (HPN). Initially, **Takagi 2002** observed these patients for mean 9.4 months on 1100 mcg Mn/day. Nine patients subsequently received 0, 110, and 55 mcg Mn/day (as $MnCl_2$) in sequential intervals each >11 months in duration. Three other patients subsequently received 110 and 55 mcg Mn/day (as $MnCl_2$) in sequential intervals each >13 months in duration. (**Takagi 2002** estimated that patients received 3-6 mcg Mn/day as PN contaminants.) Study outcomes included the (1) concentration of manganese in whole blood ($[Mn]_{WB}$; obtained approximately every month) and (2) intensity of the globus pallidum on MRI (obtained every 2-3 months).

  As shown in Table 1, MRI showed Mn excess in 0, 2, 6, and 10 patients when stabilized on 0, 55, 110, and 1100 mcg Mn/day, respectively. No patient exceeded a 24.0 mcg/L upper limit for $[Mn]_{WB}$ when stabilized on 55 mcg Mn/day (Table 1).[8] $[Mn]_{WB}$ distributed in a low normal range when patients stabilized on HPN without extra Mn. **Takagi 2002** used these results to propose 55 mcg/day as the "optimal dose of manganese" for adult HPN patients.

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[7] Prescribing Information for TRALEMENT™ (Trace Elements Injection-4, USP) for intravenous use after dilution, submitted to NDA 209376 (eCTD 0012) on September 5, 2019.

[8] 24.0 mcg/L corresponds to the maximum whole-blood Mn concentration measured by **Takagi 2012** in control bloods obtained from 46 healthy volunteers and 5 patients on an elemental diet for >1 year.

Table 1: Results from a 12-patient crossover study of manganese (Mn) supplementation during home parenteral nutrition (HPN).

Study Outcome [1]	**Mn Added Daily to HPN**			
	None N=9	**55 mcg N=12**	**110 mcg N=12**	**1100 mcg N=12**
Whole-Blood Mn [2]				
Missing	0	0	0	1
≤24.0 mcg/L	9	12	10	1
>24.0 mcg/L	0	0	2	10
MRI Intensity [3]				
Missing	0	2	0	2
None	9	8	6	0
Moderate	0	2	6	1
High	0	0	0	9

SOURCE: Takagi 2002 [31].

FOOTNOTES:

1. Mean of measurements obtained after patients stabilized on Mn dose shown (>6 months after switch).
2. A review paper by **Hardy 2008** [32] presents 3.9-15.4 mcg/L as "the most useful" normal range for Mn concentration in whole blood.
3. Intensity of globus pallidum on T1-weighted magnetic resonance imaging (MRI). Figures 2 and 3 in the source manuscript include a pre-study MRI result for a patient previously treated with Mn-supplement-free TPN.

- Between October 2007 and August 2009, **Ishizuka 2011** [33] followed 46 surgical patients (72% men; mean age 67.4 years) in Japan on total parenteral nutrition (TPN) supplemented with 0.55 mcg Mn/day. **Ishizuka 2011** measured serum manganese concentration (mean ± standard deviation, SD) at 1.4 ± 0.7, 1.4 ± 0.6, and 1.6 ± 0.5 mcg/dL (reference range 0.8-2.5 mcg/dL) in blood collected prospectively at baseline (N=46), two weeks (N=46), and four weeks (N=25), respectively. (Note; ATSDR shows the normal range for serum manganese as 0.4-0.85 mcg/L, which is equivalent to 4-8.5 mcg/dL.[9])

- Between January 2009 and March 2011, **Akutsu 2012** [34] identified 18 patients (94% men; mean age 61.6 years) starting chemotherapy in Japan for esophageal cancer. Unable to consume solids or liquids by mouth, all patients received TPN for 28 days. The first 10 patients received PN without trace-element supplements. The last 8 patients received TPN with a trace-element supplement that provided 55 mcg Mn/day. Table 2 summarizes Mn serum concentrations for each treatment group.

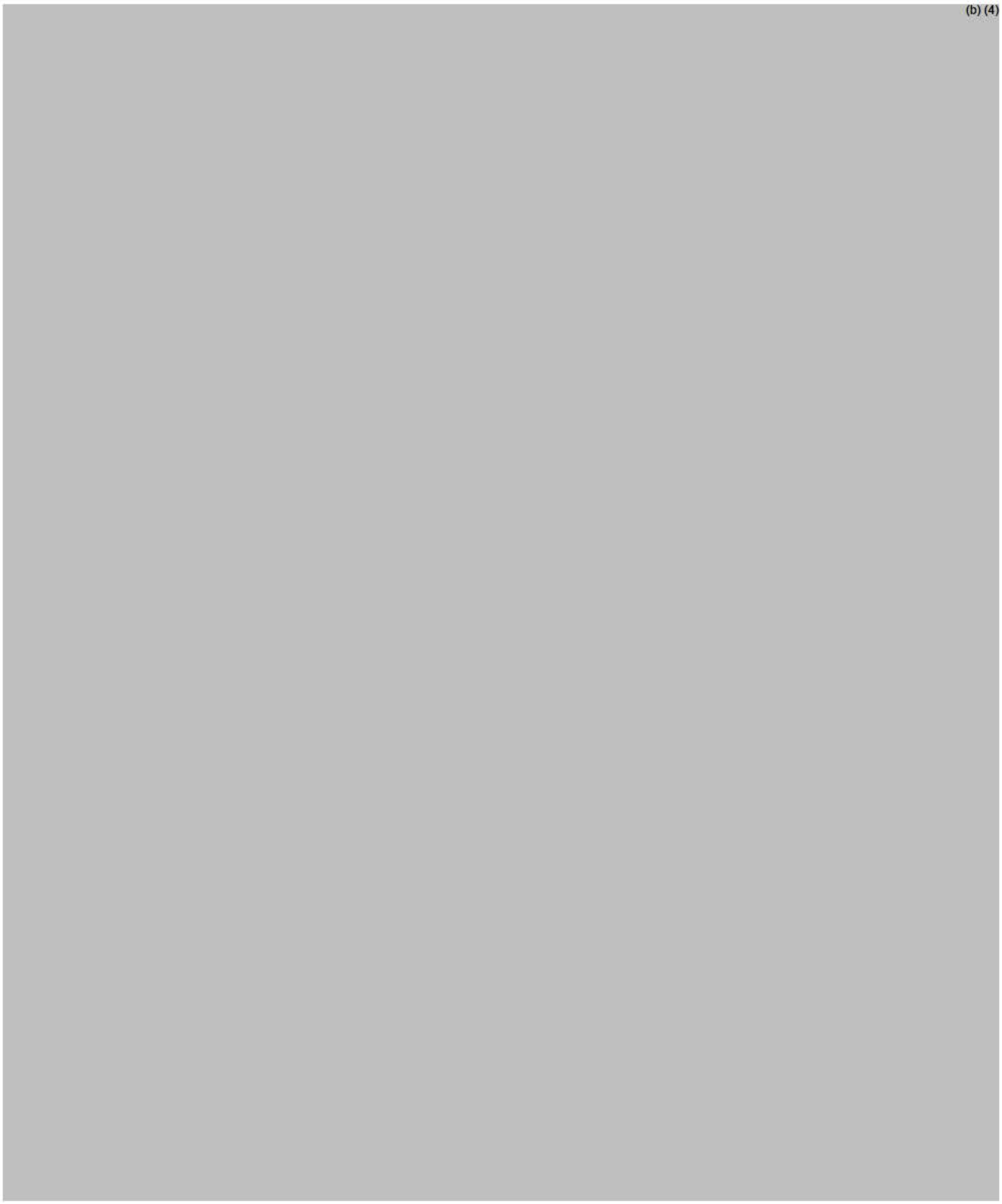
[9] Agency for Toxic Substances & Disease Registry, Toxicological Profile for Manganese, September 2012, p 8, accessed at https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=102&tid=23 on January 15, 2020.

Table 2: Results from a non-randomized study of manganese (Mn) supplementation during total parenteral nutrition (TPN).

	Mn Added Daily to PN			
	None; N=10		55 mcg; N=8	
Day on PN	**[Mn]**	**$[Mn]_{\Delta}$**	**[Mn]**	**$[Mn]_{\Delta}$**
Day 0	1.34		0.97	
Day 14	1.17	-0.17	0.90	-0.07
Day 28	1.20	-0.14	1.07	0.10

SOURCE: Akutsu 2012 [34].
ABBREVIATIONS: [Mn] – mean manganese concentration in serum; $[Mn]_{\Delta}$ – change in [Mn] from Day 0
FOOTNOTE: [Mn] and $[Mn]_{\Delta}$ possibly misreported by **Akutsu 2012** in units of mcg/mL instead of mcg/L. ATSDR shows the normal range for serum manganese as 0.4-8.5 mcg/L. See FOOTNOTE 9 to main text.

(b) (4)



4. DISCUSSION

DEPI assessed a body of medical literature (**APPENDIX 3**) to identify six study reports that might provide empirical support for Mn dosing at 55 mcg/day in adults [31,33,34] (b) (4)

(b) (4) A Mn dose-finding crossover study in 12 adults by **Takagi 2002** [31] might provide the best evidence available.[10]

Clinical efficacy studies of Mn supplementation encounter substantial difficulty because the medical community has not identified a meaningful marker for Mn deficiency. Therefore, safety considerations (driven by MRI, generally regarded as a sensitive and specific means for detecting Mn excess) drive decisions about appropriate Mn dosing for PN.

(b) (4)

FDA might regard an approval for NDA 209376 with appropriate labeling as a practical step toward satisfying requests from PN providers for safer alternatives to currently available trace-element products [4].

5 CONCLUSIONS

DEPI used a systematic approach to identify six study reports in medical literature that might support a dosing recommendation for Mn in PN.

6 RECOMMENDATIONS FOR DGIEP

Assess the six study reports listed below for evidence that might support dosing recommendations for manganese in parenteral nutrition.

- Takagi Y, Okada A, Sando K, Wasa M, Yoshida H, Hirabuki N. Evaluation of indexes of in vivo manganese status and the optimal intravenous dose for adult patients undergoing home parenteral nutrition. Am J Clin Nutr 2002;75:112-8.
- Ishizuka M, Nagata H, Takagi K, Kubota K. Sequential evaluations of trace elements in patients receiving parenteral nutrition. Hepatogastroenterology 2011;58:1466-9.
- Akutsu Y, Kono T, Uesato M, et al. Are additional trace elements necessary in total parenteral nutrition for patients with esophageal cancer receiving cisplatin-based chemotherapy? Biol Trace Elem Res 2012;150:109-15.

(b) (4)

[10] Curiously, Sponsor-commissioned or conducted literature searches missed **Takagi 2002**. DEPI identified this possibly important article in the list of references cited in **Hardy 2009** [5].

CC: Pinheiro S / Sandhu S / Hua W / Callahan C / Puigbo J / Iannacone M / Calloway P / Dunson A (OSE)

Fanti P (DPV)

Nikhar B / Meyer J / Pei Y / Navarro Almario E / Zhu Y-Y / Vu T (DGIEP)

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3. Vanek VW, Borum P, Buchman A, et al. A.S.P.E.N. position paper: recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. Nutr Clin Pract 2012;27:440-91.

4. Vanek VW, Borum P, Buchman A, et al. A Call to Action to Bring Safer Parenteral Micronutrient Products to the U.S. Market. Nutr Clin Pract 2015;30:559-69.

5. Hardy G. Manganese in parenteral nutrition: who, when, and why should we supplement? Gastroenterology 2009;137:S29-35.

6. 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;48:1324-42.

7. Safe Practices for Parenteral Nutrition Formulations. National Advisory Group on Standards and Practice Guidelines for Parenteral Nutrition. JPEN J Parenter Enteral Nutr 1998;22:49-66.

8. ASPEN Board of Directors the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr 2002;26:1SA-138SA.

9. Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. JPEN J

Parenter Enteral Nutr 2004;28:S39-70.

10. Koletzko B, Goulet O, Hunt J, et al. 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr 2005;41 Suppl 2:S1-87.

11. Osland EJ, Ali A, Isenring E, Ball P, Davis M, Gillanders L. Australasian Society for Parenteral and Enteral Nutrition guidelines for supplementation of trace elements during parenteral nutrition. Asia Pac J Clin Nutr 2014;23:545-54.

12. Pironi L, Arends J, Bozzetti F, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr 2016;35:247-307.

13. Ejima A, Imamura T, Nakamura S, Saito H, Matsumoto K, Momono S. Manganese intoxication during total parenteral nutrition. Lancet 1992;339:426.

14. Kondoh H, Iwase K, Higaki J, et al. Manganese deposition in the brain following parenteral manganese administration in association with radical operation for esophageal cancer: report of a case. Surg Today 1999;29:773-6.

15. Bertinet DB, Tinivella M, Balzola FA, et al. Brain manganese deposition and blood levels in patients undergoing home parenteral nutrition. JPEN J Parenter Enteral Nutr 2000;24:223-7.

16. Orimo S, Ozawa E. Short-term administration of an essential trace elements preparation (Elemenmic) causes a high whole blood manganese concentration and manganese deposition in basal ganglia. Intern Med 2001;40:1162-3.

17. Takagi Y, Okada A, Sando K, Wasa M, Yoshida H, Hirabuki N. On-off study of manganese administration to adult patients undergoing home parenteral nutrition: new indices of in vivo manganese level. JPEN J Parenter Enteral Nutr 2001;25:87-92.

18. Iwase K, Higaki J, Mikata S, et al. Manganese deposition in basal ganglia due to perioperative parenteral nutrition following gastrointestinal surgeries. Dig Surg 2002;19:174-83.

19. Abdalian R, Saqui O, Fernandes G, Allard JP. Effects of manganese from a commercial multi-trace element supplement in a population sample of Canadian patients on long-term parenteral nutrition. JPEN J Parenter Enteral Nutr 2013;37:538-43.

20. Dastych M, Dastych M, Jr., Senkyrik M. Manganese in whole blood and hair in patients with long-term home parenteral nutrition. Clin Lab 2016;62:173-7.

21. Jin J, Saqui O, Allard JP. Effect of discontinuation of manganese supplementation from home parenteral nutrition solutions on whole-blood levels and magnetic resonance imaging of the brain: A 5-year cohort study. JPEN J Parenter Enteral Nutr 2018;42:164-70.

22. Ono J, Harada K, Kodaka R, et al. Manganese deposition in the brain during long-term total parenteral nutrition. JPEN J Parenter Enteral Nutr 1995;19:310-2.

23. Fell JM, Reynolds AP, Meadows N, et al. Manganese toxicity in children receiving long-term parenteral nutrition. Lancet 1996;347:1218-21.

24. Iinuma Y, Kubota M, Uchiyama M, et al. Whole-blood manganese levels and brain manganese accumulation in children receiving long-term home parenteral nutrition. Pediatr Surg Int 2003;19:268-72.

25. Aschner JL, Anderson A, Slaughter JC, et al. Neuroimaging identifies increased manganese deposition in infants receiving parenteral nutrition. Am J Clin Nutr 2015;102:1482-9.

26. Mehta R, Reilly JJ. Manganese levels in a jaundiced long-term total parenteral nutrition patient: potentiation of haloperidol toxicity? Case report and literature review. JPEN J Parenter Enteral Nutr 1990;14:428-30.

27. Mirowitz SA, Westrich TJ, Hirsch JD. Hyperintense basal ganglia on T1-weighted MR images in patients receiving parenteral nutrition. Radiology 1991;181:117-20.

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29. Nagatomo S, Umehara F, Hanada K, et al. Manganese intoxication during total parenteral nutrition: report of two cases and review of the literature. J Neurol Sci 1999;162:102-5.

30. Dickerson RN. Manganese intoxication and parenteral nutrition. Nutrition 2001;17:689-93.

31. Takagi Y, Okada A, Sando K, Wasa M, Yoshida H, Hirabuki N. Evaluation of indexes of in vivo manganese status and the optimal intravenous dose for adult patients undergoing home parenteral nutrition. Am J Clin Nutr 2002;75:112-8.

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34. Akutsu Y, Kono T, Uesato M, et al. Are additional trace elements necessary in total parenteral nutrition for patients with esophageal cancer receiving cisplatin-based chemotherapy? Biol Trace Elem Res 2012;150:109-15.

(b) (4)


(b) (4)

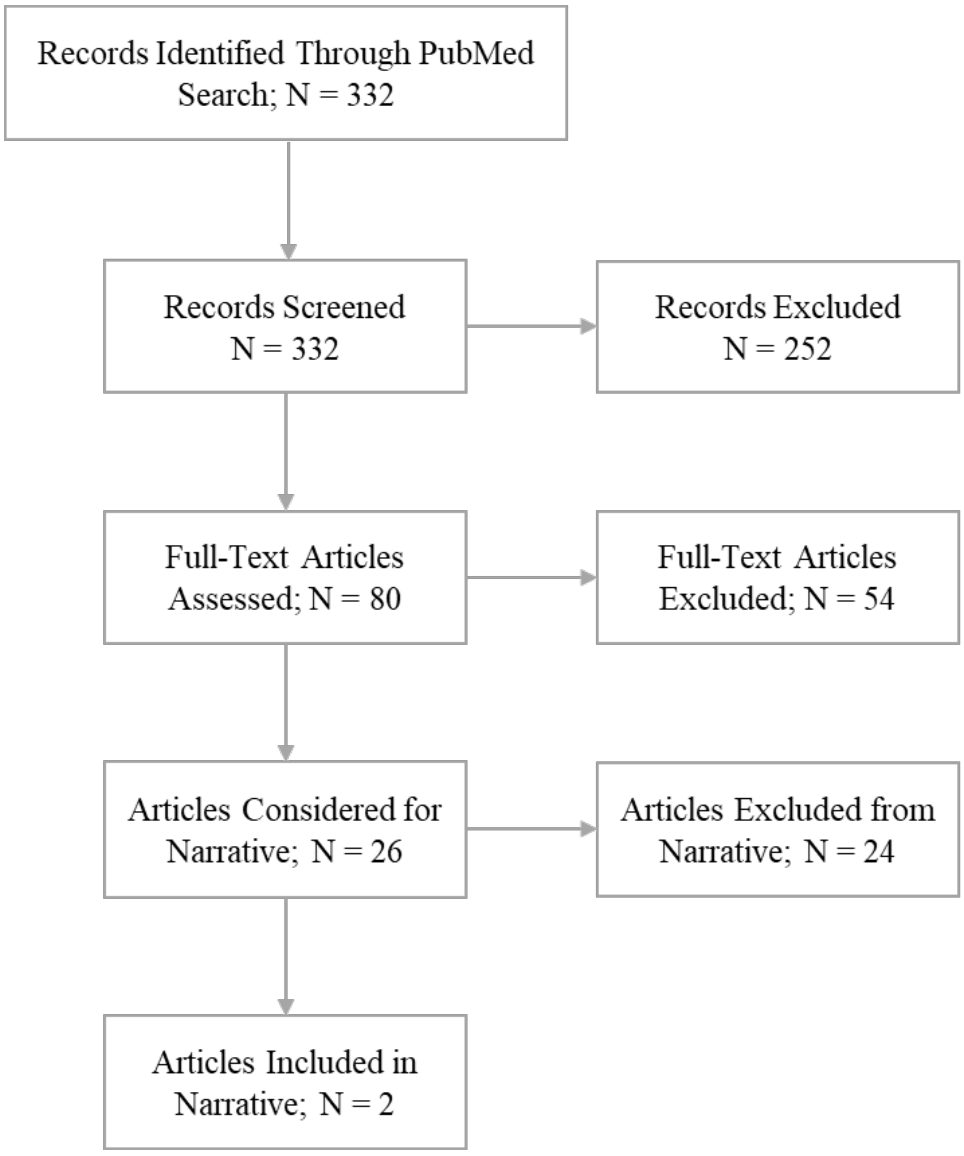
APPENDIX 1: DEPI supplemental literature search

On November 27, 2019, DEPI used (b) (4) query language, reproduced below, to update a (b) (4) PubMed search conducted on December 22, 2015. DEPI's search retrieved 332 PubMed records for articles published in 2015 or later.

(b) (4)

As summarized in Appendix Figure 1, a DEPI analyst (JLW) screened the titles and abstracts for these 332 PubMed records to select 80 articles for full-text examination. The full-text examination identified 26 full-text articles with results from original research (1) in patients given Mn parenterally or (2) about Mn status in patients on parenteral nutrition (**APPENDIX 2**). DEPI included two articles in the review narrative [36,37].

Appendix Figure 1: PRISMA Flow Diagram



FOOTNOTE: See **APPENDIX 2** for lising of articles considered for narrative.

APPENDIX 2: Possibly informative articles identified by DEPI PubMed search

Bolded text identifies articles discussed by DEPI in the review narrative. Underlined text identifies additional articles referenced in NDA 209376.

1. Amin H, Shawkat A. Manganese toxicity complicating parenteral nutrition. Am J Ther 2019:10.1097/MJT.0000000000000899.

2. Aschner JL, Anderson A, Slaughter JC, et al. Neuroimaging identifies increased manganese deposition in infants receiving parenteral nutrition. Am J Clin Nutr 2015;102:1482-9.

3. Braga CB, Ferreira IM, Marchini JS, Cunha SF. Copper and magnesium deficiencies in patients with short bowel syndrome receiving parenteral nutrition or oral feeding. Arq Gastroenterol 2015;52:94-9.

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9. Freitas R, Hessel G, Cozzolino SMF, et al. Inflammatory process of patients receiving parenteral nutrition is not exclusively responsible for low selenium and glutathione peroxidase levels. Nutrition 2019;61:202-7.

10. Fukatsu K, Shineha R, Kawauchi Y, Saeki M, Nakayama M. Optimizing vitamin and trace element profiles in blood after gastrointestinal tract surgery by a new parenteral nutrition formula. Ann Nutr Metab 2019;74:189-99.

11. [redacted] (b) (4)

12. Gupta K, Wang H, Amin SB. Copper supplementation in premature infants with parenteral nutrition-associated cholestasis. Nutr Clin Pract 2018;33:718-24.

13. Hines EQ, Soomro I, Howland MA, Hoffman RS, Smith SW. Massive intravenous manganese overdose due to compounding error: Minimal role for hemodialysis. Clin Toxicol (Phila) 2016;54:523-5.

14. Hortencio TDR, Arendt BM, Teterina A, et al. Changes in home parenteral nutrition practice based on the Canadian Home Parenteral Nutrition Patient Registry. JPEN J Parenter Enteral Nutr 2017;41:830-6.

15. Jafari P, Thomas A, Haselbach D, et al. Trace element intakes should be revisited in burn nutrition protocols: A cohort study. Clin Nutr 2018;37:958-64.

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17. [redacted] (b) (4)

18. Kirk C, Gemmell L, Lamb CA, Thompson NP, Mountford CG, Toole BJ. Elevated whole-blood manganese levels in adult patients prescribed "manganese-free" home parenteral nutrition. Nutr Clin Pract 2019:10.1002/ncp.10431.

19. Leite HP, Koch Nogueira PC, Uchoa K, Carvalho de Camargo MF. Copper deficiency in children with intestinal failure: Risk factors and influence on hematological cytopenias. JPEN J Parenter Enteral Nutr 2019:10.1002/jpen.728.

20. Liu M-Y, Tang H-C, Hu S-H, Yang H-L, Chang S-J. Influence of preoperative peripheral parenteral nutrition with micronutrients after colorectal cancer patients. BioMed research international 2015;2015:535431.

21. Palm E, Dotson B. Copper and zinc deficiency in a patient receiving long-term parenteral nutrition during a shortage of parenteral trace element products. JPEN J Parenter Enteral Nutr 2015;39:986-9.

22. Prasad R, Hawthorne B, Durai D, McDowell I. Zinc in denture adhesive: a rare cause of copper deficiency in a patient on home parenteral nutrition. BMJ Case Rep 2015;2015:bcr2015211390.

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APPENDIX 3: Articles assessed by DEPI

Adult population (sorted by year of publication and author name)

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology Review of Study Protocol

Date:	December 23, 2019
Reviewer:	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Acting Team Leader:	Catherine Callahan, PhD MA Division of Epidemiology I
Deputy Director:	CAPT. Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Drug Name:	Trace Elements Injection-4 (Tralement™)
Subject:	Medical literature supporting parenteral nutrition guidelines for copper dosing
Application Type/Number:	NDA 209376
Applicant/sponsor:	American Regent (formerly Luitpold Pharmaceuticals)
OSE RCM #:	2019-1925

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Responding to a request from the Division of Gastroenterology and Inborn Error Products (DGIEP), the Division of Epidemiology I (DEPI) identified study reports in medical literature that might support a dosing recommendation for copper (Cu) in parenteral nutrition (PN).

The request from DGIEP concerns Trace Elements Injection-4 (NDA 209376), a trace-element PN additive containing selenium (as selenious acid), zinc (as zinc sulfate heptahydrate), copper (as cupric sulfate), and manganese (as manganese sulfate monohydrate).

DEPI used a systematic approach to identify 16 study reports in medical literature that FDA might use to support a dosing recommendation for Cu in PN. DEPI's approach identified two types of studies, (1) pivotal studies of Cu balance in patients receiving Cu-supplemented PN and (2) supportive studies describing biochemical outcomes in patients receiving PN that contained well specified amounts of Cu.

DEPI recommended that DGIEP consider the study reports identified by DEPI as a source of evidence that might support a dosing recommendation for copper in parenteral nutrition.

1 INTRODUCTION

Responding to a request from the Division of Gastroenterology and Inborn Error Products (DGIEP), the Division of Epidemiology I (DEPI) identifies study reports in medical literature that might support a dosing recommendation for copper (Cu) in parenteral nutrition (PN).

The request from DGIEP concerns Trace Elements Injection-4 (NDA 209376), a trace-element PN additive containing selenium (as selenious acid), zinc (as zinc sulfate heptahydrate), copper (as cupric sulfate), and manganese (as manganese sulfate monohydrate).

The Sponsor seeks approval for Trace Elements Injection-4 through a 505(b)(2) literature-only pathway. To identify relevant literature, the Sponsor commissioned a systematic literature review, conducted by (b) (4) DEPI previously validated the (b) (4) search in reviews completed for Selenious Acid Injection (NDA 209379) and Zinc Sulfate Injection (NDA 209377).[1]

On September 16, 2019, DGIEP requested "DEPI consultation on the methodology and approach in literature submitted to support the efficacy and safety of Selenious Acid, Zinc Sulfate, Copper and Manganese."[2] During a meeting on November 13, 2019, DGIEP agreed to limit this request

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[1] Weissfeld JL, Bright PL, Sandhu SK. Evaluation of a Systematic Review of Medical Literature: Selenious Acid for Parenteral Nutrition, filed under NDA 209379 on March 12, 2019 (DARRTS Reference ID: 4402464).

Weissfeld JL, Bright PL, Sandhu SK. Evaluation of a Systematic Review of Medical Literature: Zinc Sulfate for Parenteral Nutrition, filed under NDA 209377 on April 30, 2019 (DARRTS Reference ID: 4426323).

[2] Request for Consultation filed under NDA 209376 on September 16, 2019 (DARRTS Reference ID: 4492272).

to cover study reports in medical literature that might support recommendations in FDA labels for copper and manganese in parenteral nutrition (PN) with respect to optimal dosing for efficacy and safety. This review concerns copper. DEPI plans a separate review for manganese.[3]

2 REVIEW METHODS AND MATERIALS

2.1 Documents reviewed

Reference	Date	Title
(b) (4) Report - Adults	2016-JUN-10	Systematic Literature Review for Trace Elements in Parenteral Nutrition: Copper in the Adult Population, submitted to NDA 209377 (eCTD 0002) on October 22, 2018.
(b) (4) Report - Pediatric	2016-JUN-10	Systematic Literature Review for Trace Elements in Parenteral Nutrition: Copper in the Pediatric Population, submitted to NDA 209377 (eCTD 0002) on October 22, 2018.
Clinical Overview - Adult	2017-OCT-14	Clinical Overview for Trace Element Injection (Adult), submitted to NDA 209376 (eCTD 0003) on October 12, 2018.
Clinical Overview - Pediatric	2017-OCT-14	Clinical Overview for Trace Element Injection (Pediatric), submitted to NDA 209376 (eCTD 0003) on October 12, 2018.
SCE - Adult	2017-OCT-14	Summary of Clinical Efficacy for Trace Element Injection (Adult), submitted to NDA 209376 (eCTD 0003) on October 12, 2018.
SCE - Pediatric	2017-OCT-14	Summary of Clinical Efficacy for Trace Element Injection (Pediatric), submitted to NDA 209376 (eCTD 0003) on October 12, 2018.
SCS - Adult	2017-OCT-14	Summary of Clinical Safety for Trace Element Injection (Adult), submitted to NDA 209376 (eCTD 0003) on October 12, 2018.
SCS - Pediatric	2017-OCT-14	Summary of Clinical Safety for Trace Element Injection (Pediatric), submitted to NDA 209376 (eCTD 0003) on October 12, 2018.
Draft Label	2019-SEP-04	Prescribing Information for TRALEMENT™ (Trace

[3] For reviews completed by FDA to establish selenium and zinc PN dosing, see

UniReview: A Multi-Disciplinary Review and Evaluation for Selenious Acid, filed under NDA 209379 on March 2, 2019 (DARRTS Reference ID: 4427655).

UniReview: A Multi-Disciplinary Review and Evaluation for Selenious Acid, filed under NDA 209377 on July 18, 2019 (DARRTS Reference ID: 4464465).

Reference	Date	Title
		Elements Injection-4), submitted to NDA 209376 (eCTD 0012) on September 5, 2019.
Clinical Information Amendment	2019-DEC-06	Clinical Information Amendment - Response to 74-Day Letter: No Filing Review Issues Identified, submitted to NDA 209376 (eCTD 0017) on December 6, 2019.

2.2 Review methods

DEPI identified source literature about Cu dosing for PN by examining articles (1) identified by (b) (4) systematic literature search, (2) discussed by the Sponsor in documents submitted to NDA 209376, (3) referenced in guideline statements, review articles, or book chapters, and (4) identified by independent PubMed search (**APPENDIX 1**).

3 REVIEW RESULTS

3.1 Dosing guideline in draft label for Trace Elements Injection-4

Each mL of Trace Elements Injection-4 contains 0.3 mg copper (Cu) as cupric sulfate. For patients on parenteral nutrition (PN), the draft label for Trace Elements Injection-4 recommends dosing adults (b) (4) at 1 mL per day (b) (4) .[4] These recommendations correspond to Cu dosing in adults (b) (4) 0.3 mg/day (b) (4)

(b) (4)

3.2 Dosing guidelines in medical literature

In 1979, the Nutrition Advisory Group (NAG) for the American Medical Association (AMA) Department of Foods and Nutrition published guidelines for essential trace element preparations intended for parenteral use [1]. This group used expert opinion, clinical experience, and results from balance studies to suggest intravenous (IV) Cu intakes of 0.5-1.5 mg/day in adult patients and 20 mcg/kg/day in pediatric patients.

In 1998, the American Society for Parenteral and Enteral Nutrition (ASPEN) published guidelines for safe PN practice [2]. ASPEN established standard ranges for Cu supplementation in PN patients with normal organ function, (1) 0.3-0.5 mg/day for adults, (2) 0.2-0.5 mg/day for older (≥5-year-old) children and adolescents, and (3) 20 mcg/kg/day for preterm neonates, term

[4] Prescribing Information for TRALEMENT™ (Trace Elements Injection-4, USP) for intravenous use after dilution, submitted to NDA 209376 (eCTD 0012) on September 5, 2019.

neonates, and younger (<5-year-old) children. More recent guidelines from several organizations align with these 1998 ASPEN standards [3-11].

3.3 Rationale for dosing guidelines

3.3.1 Adults, adolescents, and older children

The Sponsor presents three lines of evidence to support Cu 0.3 mg/day for IV dosing in adults on PN.[5]

- The Sponsor assumes 35% bioavailability for dietary copper. The adult U.S. Recommended Daily Allowance (RDA) for dietary copper is 0.9 mg/day.[6] Together, these statements suggest 0.315 mg/day as the amount of copper required intravenously in adults who depend entirely on PN.

- Referencing four controlled studies [12-16], the Sponsor asserts that adult PN doses "as low as 0.3 mg/day of copper have been shown to increase serum copper concentrations."

- The Sponsor references **Shike 1981** [17] (reviewed by DEPI, below) to claim that "copper 0.3 mg/day is required to achieve copper balance in adult patients maintained on PN."

In a review article prepared for the New York Academy of Medicine, **Shike 1984** [18] recommended maintenance PN dosing for Cu at (1) 0.3 mg/day in adults, (2) 0.2 mg/day in children, and (3) 0.5 mg/day in patients with gastrointestinal secretions greater than 300 gm/day. These recommendations from **Shike 1984** and the standard adopted in 1998 by ASPEN for adults, adolescents, and older children align perfectly.

Shike 1984 cited five supporting clinical studies under a section heading titled, **Requirements by Intravenous Routes**.

- **Jacobson 1977** [19] administered between 0.23 and 0.29 mg Cu IV daily for 5 days to four adult men on total PN (TPN). The Cu amounts administered in three of four patients exceeded losses measured in urine, feces, and gastric secretions. **Jacobson 1977** suggested that Cu 0.1 mg/day might replace normal losses during TPN.

- Reporting in French, **Ricour 1977** [20] observed normal Cu concentrations ([Cu]) in plasma collected from six children (including at least four infants) on TPN providing Cu 20

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[5] Luitpold Pharmaceuticals, Summary of Clinical Efficacy for Trace Element Injection (Adult), submitted to NDA 209376 (eCTD 0003) on October 12, 2018, pages 210-211.

[6] Institute of Medicine, Copper (https://www.nap.edu/read/11537/chapter/34), in Dietary Reference Intakes: The Essential Guide to Nutrient Requirements, The National Academies Press, Washington, D.C., 2006.

mcg/kg/day.[7]

- **Lowry 1981** [12] measured serum [Cu] before and during 33 episodes of TPN in 24 cancer patients. Twenty patients (ages 10-69 years) with 29 TPN episodes received Cu at doses much higher than the 1998 ASPEN standard.

- **Phillips 1981** [21] achieved positive Cu balance in 6 of 8 PN patients (ages 40-70 years) given Cu 0.5 and 0.75 mg/day for 7 days.

- **Shike 1981** [17] assessed Cu balance in a 3-week randomized crossover study of Cu supplementation in 24 TPN patients (ages 15-73 years, weight 39-84 kg). **Shike 1981** regarded 23 patients as mildly and one patient as severely malnourished. **Shike 1981** estimated the mean Cu received as contaminants in TPN solutions at 0.25 mg/day. Each patient received Cu (as copper chloride) supplemented IV at 0, 0.8, and 1.6 mg/day for randomly ordered 7-day periods. On average, patients achieved neutral Cu balance (intakes matching losses in urine, stool, and other gastrointestinal sources) when supplemented at 0 mg/day (total exposure 0.25 mg/day). Patients demonstrated positive Cu balance (intakes greater than losses) when supplemented at 0.8 or 1.6 mg/day (total exposure 1.05 or 1.85 mg/day). Mean Cu loss through all gastrointestinal routes was 0.12 mg/day higher (0.34 *vs.* 0.22 mg/day) on days with high fecal and gastrointestinal fluid loss (>300 gm/day) *vs.* days with low fecal and gastrointestinal fluid loss (≤300 gm/day). Mean Cu loss through all gastrointestinal routes was 0.13 mg/day lower (0.08 *vs.* 0.21 mg/day) in six patients with cholestasis (elevated blood alkaline phosphatase) than in 18 patients without cholestasis. **Shike 1981** used these results to identify 0.3 mg/day as the "amount of copper required to achieve balance in adult patients maintained on TPN." **Shike 1981** extended this basic result by recommending 0.4-0.5 mg/day in patients with "diarrhea or excessive fluid losses through gastrointestinal stomas or fistulas" and 0.15 mg/day in patients with "abnormalities of the liver excretory system." **Shike 1981** concluded that higher Cu doses for long periods might "result in a significant accumulation of surplus copper with deposition in liver, brain, and other tissues, and possibly damage as a result."

3.3.2 Preterm infants, term infants, and younger children

In a report prepared for the American Society for Clinical Nutrition (ASCN) Committee on Clinical Practice Issues, **Greene 1988** [3] endorsed the 1979 NAG-AMA Cu guideline (20 mcg/kg/day) for pediatric patients on PN [1]. Citing a book chapter by **Casey and Hambidge 1985** [22], **Greene 1988** set the metabolic Cu requirement in intravenously fed preterm and young term infants at 35 mcg/kg/day. **Greene 1988** justified this requirement by the amounts needed to (1) replace Cu lost in urine (5 mcg/kg/day), (2) replace Cu lost in feces (10 mcg/kg/day), and (3) supply Cu for extrahepatic tissue growth (20 mcg/kg/day). Because of the

[7] This bullet corrects an erroneous statement in **Shike 1984**. **Shike 1984** erroneously stated that **Ricour 1977** observed copper plasma levels in "10 children between the ages of two and eight years."

"significant hepatic Cu stores" available to even "the very premature infant," **Greene 1988** judged the 1979 NAG-AMA Cu standard (20 mcg/kg/day) as "probably at least adequate for premature infants and for young infants born at term." **Greene 1988** extended the NAG-AMA standard to younger children by asserting "plasma Cu levels are normal in children aged to 2-8 y when Cu is added in an amount of 20 µg Cu/kg." **Greene 1988** suggested a Cu PN requirement of 30-35 mcg/kg/day for "patients with jejunostomies or exterior biliary drainage." Finally, **Greene 1988** advised "considerable caution … in administering intravenous Cu to patients with impaired biliary excretion including those with TPN cholestasis."

3.4 Supporting evidence

DEPI summarizes additional supporting evidence (1) identified by (b) (4) systematic literature search, (2) referenced in documents submitted by the Sponsor, (3) referenced in guideline statements, review articles, or book chapters [1-4,7-10,18,22,25-28], or (4) identified by independent PubMed search (**APPENDIX 1**).

3.4.1 Adults

- Between October 2007 and August 2009, **Ishizuka 2011** [29] followed 46 surgical patients (mean age 67.4 years) on TPN with Cu 0.3 mg/day. **Ishizuka 2011** measured serum [Cu] (mean ± standard deviation, SD) at 119 ± 32, 111 ± 26, and 113 ± 23 mcg/dL (reference range 68-128 mcg/dL) in blood collected prospectively at baseline (N=46), two weeks (N=46), and four weeks (N=25), respectively.

- **Dastych 2016** [30] collected blood from 68 patients (age 28-68 years) on home PN for 4 to 96 months. PN during the previous three months contained Cu supplemented at median 0.9

[8] Luitpold Pharmaceuticals, Summary of Clinical Efficacy for Trace Element Injection (Pediatric), submitted to NDA 209376 (eCTD 0003) on October 12, 2018, pages 122-124.

mg/day (interquartile range, IQR, 0.67-1.30 mg/day). **Dastych 2016** measured [Cu] at median 102 mcg/dL (IQR 88-123 mg/dL) in the PN group and median 95 mcg/dL (IQR 92-112 mcg/dL) in a control group (10 healthy hospital employees, age 25-65 years).

- **Uzzan 2017** [31] used January-June 2013 data in a registry of home PN patients at a tertiary care center to identify 73 patients (mean age 49 years, range 18-86 years) on stable PN for at least one month. The first Cu IV dose recorded during the study period averaged 0.31 mg/day (SD 0.08 mg/day). Serum [Cu] (available for 72 patients) averaged 105 mcg/dL (SD 38 mcg/dL). **Uzzan 2017** identified 10 (13.9%) and 9 (12.5%) patients with serum [Cu] below and above the reference range (81-141 mcg/dL), respectively.

3.4.2 Children

- **James 1976** [32] conducted 24-hour or 48-hour nutritional balance studies (N=26) in four premature infants (birth weight <1050 gm) gaining weight on TPN. Fecal output never occurred during a balance study. The variable results shown for Cu (Figure 1) identified 17 mcg/kg/day as the minimum Cu amount possibly needed IV to replace Cu lost in urine.

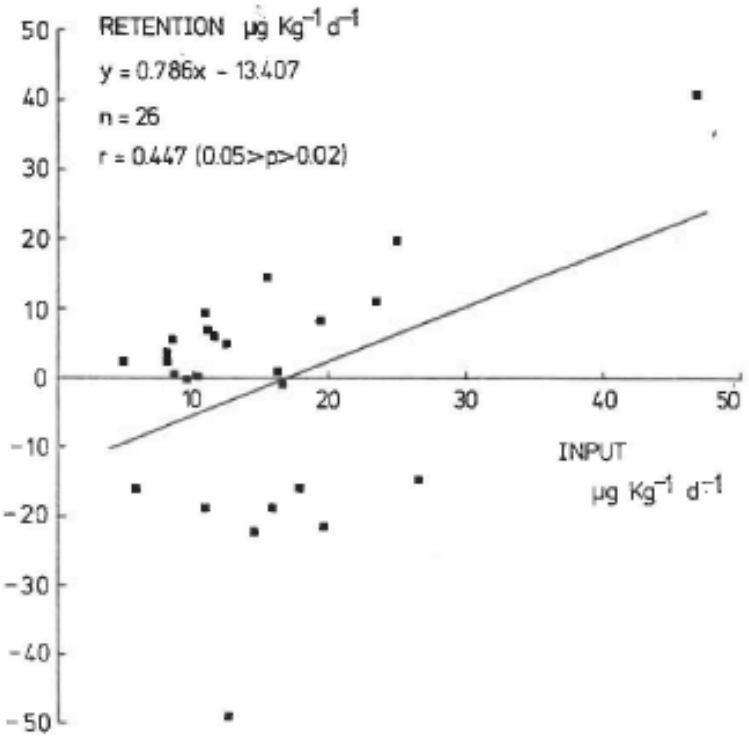

Figure 1: Copper input *vs.* retention results from 26 balance studies in four premature infants on TPN. Source: Figure 8 in **James 1976** [32].

- **Zlotkin 1983** [33] conducted 72-hour trace-element balance studies in 38 infants stabilized on TPN with Cu dosed variably as copper chloride. The study group included (1) 15 preterm infants (mean birth weight 1124 gm), (2) 8 small-for-gestational-age full-term infants (mean

birth weight 2240 gm), and (3) 15 normal weight full-term infants (mean birth weight 3148 gm). As shown in Figure 2, **Zlotkin 1983** estimated (1) 16 mcg/kg/day as the Cu amount needed IV to replace Cu lost in urine, stool, and nasogastric aspirate and (2) 63 mcg/kg/day as the Cu amount needed IV to match the Cu retained daily by a fetus growing *in utero* "along the 50th percentile" (50 mcg/kg/day [34]).

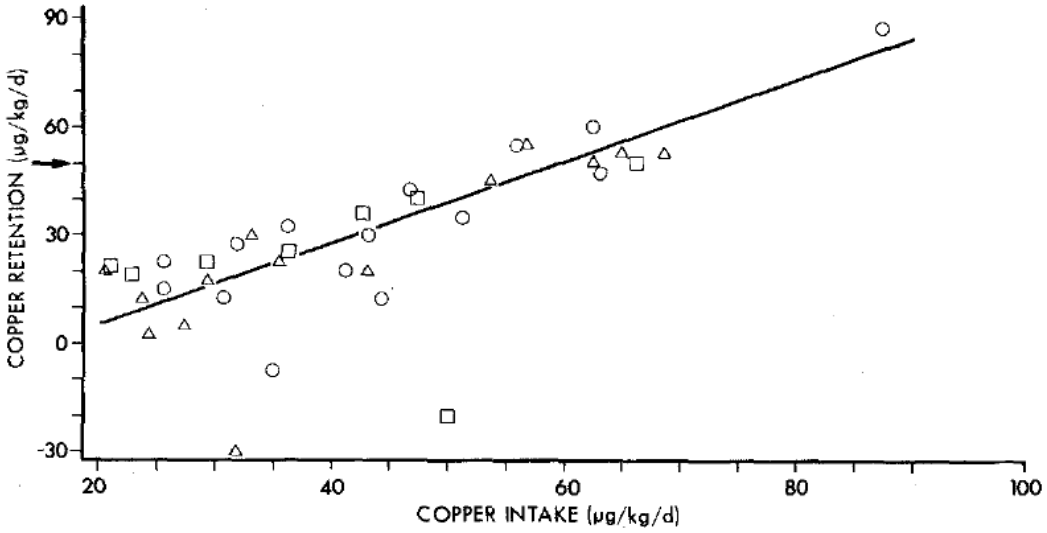

Figure 2: Copper input *vs.* retention results from TPN balance studies in 38 infants (circle - premature, triangle - full-term, square - full-term small for gestational age). Source: Figure 2 in **Zlotkin 1983** [33].

- **Suita 1984** [35] randomized post-surgical newborn infants (12 full-term, 10 premature) to TPN with Cu 20 mcg/kg/day added after either (1) 1-week delay (N=12; TPN duration 22-576 days) or (2) 4-week delay (N=10; TPN duration 21-223 days). (TPN solutions contained 5-6 mcg/dL.) On day 270, Cu deficiency (anemia, osteopenia, and plasma [Cu] 32 mcg/dL) developed in a full-term infant from the early (1-week delay) Cu group.

- **Lockitch 1983** [36] randomized N=127 low birth-weight infants (<2500 gm) to PN with Cu 20 or 40 mcg/kg/day. **Lockitch 1983** observed statistically similar serum [Cu] trends in infants (N=72) maintained on Cu 20 or 40 mcg/kg/day for at least 11 days (Table 1).

Table 1: Mean serum copper concentration and standard deviation (SD; mcg/dL) at birth, 1 week, and 2 weeks in low birth-weight infants on parenteral nutrition with copper 20 or 40 mcg/kg/day.

	Birth		1 week		2 weeks	
Copper Dose Group	Mean	SD	Mean	SD	Mean	SD
20 mcg/kg/week (N=40)	41	16	36	14	35	14
40 mcg/kg/week (N=32)	36	15	36	11	42	16

Source: Table IV in **Lockitch 1983** [36].

- **Frem 2010** [37] used hospital records to identify 28 premature infants (mean gestational age 30 weeks, mean birth weight 1550 gm) who developed cholestasis (direct bilirubin

concentration ≥2 mg/dL) after ≥1 month PN with standard-dose Cu (20 mcg/kg/day). Per hospital policy, these cholestatic infants continued on standard Cu-dose PN with no demonstrable worsening in liver function.

- **Gupta 2018** [38] used hospital records to identify 24 premature infants (mean gestational age 28.6 weeks, mean birth weight 1260 gm) who developed cholestasis (direct bilirubin concentration ≥2 mg/dL) after mean 28 days on PN with standard-dose Cu (≈20 mcg/kg/day). Per hospital policy, infants subsequently received Cu intermittently (20 mcg/kg 2-4 times per week). **Gupta 2018** identified no meaningful changes in hematologic or hepatic laboratory values after mean 39, 54, and 63 days of intermittent Cu in 24, 12, and 6 infants, respectively.

4. DISCUSSION

Guidelines for dosing Cu during PN seek to prevent deficiency (manifesting as anemia, neutropenia, or osteopenia) in patients with sufficient hepatic stores at start of treatment. Achieving this objective requires doses high enough to (1) replace normal losses in urine and feces and (2) possibly nourish growing tissues in infants and young children, yet low enough to (3) avoid toxic injury through excessive hepatic accumulation.

Dietary studies provide limited guidance for dosing Cu during PN. Humans control Cu stores by regulating intestinal absorption, a control mechanism bypassed by IV Cu. Biliary and urinary excretion controls Cu stores less effectively. The absence of laboratory bioassays for Cu stores further impairs efforts to define adequate or optimal Cu doses for PN.

Therefore, current guidelines principally rely on studies of Cu balance in patients on PN. Studies using other outcomes (*e.g.*, preventing deficiency or maintaining [Cu] within a normal laboratory range) offer supportive evidence only.

A guideline published in 1998 by ASPEN [2] established the enduring standard ranges for Cu supplementation during PN. DEPI presumes that ASPEN chose these standard ranges by using a scientific reasoning presented in review articles published in 1984 [18] and 1988 [3].

DEPI lists in Table 2 the published study reports that FDA might use to support an adult or pediatric dosing recommendation for Cu in PN. These study reports provide the types of evidence review authors used in 1984 [18] and 1988 [3] to support a science-based rationale for Cu dosing in adult and pediatric patients, respectively. Table 2 lists two types of studies, (1) pivotal studies of Cu balance in patients receiving Cu-supplemented PN [17,32,33] and (2) supportive studies describing biochemical outcomes in patients receiving PN that contained well specified amounts of Cu [12,19-21,23,24,29-31,35-38]. Table 2 excludes other types of studies of possible interest, such as reports of Cu deficiency in patients on PN not supplemented with copper.

Table 2: Study reports in medical literature that might support an FDA dosing recommendation for copper (Cu) in parenteral nutrition (PN). Bolded type

identifies pivotal studies of Cu balance in patients receiving Cu-supplemented PN.

Author Year	Source	Country	N	NDA Reference
Adult Literature				
Jacobson 1977 [19]	Other	Sweden	4	
Lowry 1981 [12]	NDA	U.S.	20	SCE Table 16
Phillips 1981 [21]	Other	Australia	8	
Shike 1981 [17]	NDA	Canada	28	SCE Table 16
Ishizuka 2011 [29]	NDA	Japan	46	SCE Table 21
Dastych 2016 [30]	NDA	Czech Republic	68	CIA
Uzzan 2017 [31]	NDA	France	73	CIA
Pediatric Literature				
James 1976 [32]	Other	Australia	4	
Ricour 1977 [20]	Other	France	6	
Zlotkin 1983 [33]	Other	Canada	38	
Friel 1984 [23]	NDA	Canada	22	SCE Table 15
Suita 1984 [35]	NDA	Japan	22	SCE Table 15
Lockitch 1983 [36]	Other	Canada	72	
Frem 2010 [37]	Other	U.S.	28	
MacKay 2015 [24]	NDA	U.S.	751	SCE Table 15
Gupta 2018 [38]	NDA	U.S.	24	CIA

ABBREVIATIONS: CIA – Clinical Information Amendment; SCE – Summary of Clinical Efficacy. LEGEND: Source – means of discovery (NDA or Other Source); N – number of study patients treated with Cu IV.

The 1998 ASPEN guideline established standard dose ranges for Cu in PN patients with normal organ function at,

- 0.3-0.5 mg/day in adults.
- 0.2-0.5 mg/day in older (≥5-year-old) children and adolescents.
- 20 mcg/kg/day in preterm neonates, term neonates, and younger (<5-year-old) children.

The labeling proposed by the Sponsor (b) (4)

- Adults (b) (4) at 1 mL/day (0.3 mg/day).
- (b) (4)
-

(b) (4)

For typical patients on chronic TPN, these low-end dosing recommendations appear designed to prevent overt deficiency while optimally protecting against excessive hepatic accumulation. As a reason for concern, two often cited articles describe high hepatic Cu in patients after long-term PN [39,40].

DEPI's survey of medical literature uncovered no reports of clinical toxicity attributable to Cu for PN. **Murphy 2017** [41] presented two case reports of compounding errors resulting in the unintended administration (without apparent adverse consequence) of (1) Cu 23.3 mcg/kg/day instead of 13.3 mcg/kg/day for one week in a 10-year old-boy and (2) Cu 56 mcg/kg/day instead of 16 mcg/kg/day for two months in a 12-month-old girl.

5 CONCLUSIONS

DEPI used a systematic approach to identify 16 study reports in medical literature that FDA might use to support a dosing recommendation for Cu in PN. DEPI's approach identified two types of studies, (1) pivotal studies of Cu balance in patients receiving Cu-supplemented PN [17,32,33] and (2) supportive studies describing biochemical outcomes in patients receiving PN that contained well specified amounts of Cu [12,19-21,23,24,29-31,34-37].

6 RECOMMENDATIONS FOR DGIEP

Consider the study reports identified by DEPI as a source of evidence that might support a dosing recommendation for copper in parenteral nutrition.

CC: Pinheiro S / Sandhu S / Hua W / Callahan C / Iannacone M / Billings M / Calloway P / Dunson A (OSE)

Fanti P (DPV)

Nikhar B / Meyer J / Pei Y / Navarro Almario E / Zhu Y-Y / Vu T (DGIEP)

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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;48:1324-42.

4. ASPEN Board of Directors the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr 2002;26:1SA-138SA.

5. Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. JPEN J Parenter Enteral Nutr 2004;28:S39-70.

6. Koletzko B, Goulet O, Hunt J, et al. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr 2005;41 Suppl 2:S1-87.

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23. Friel JK, Gibson RS, Peliowski A, Watts J. Serum zinc, copper, and selenium concentrations in preterm infants receiving enteral nutrition or parental nutrition supplemented with zinc and copper. J Pediatr 1984;104:763-8.

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with deficiencies, a retrospective study from a tertiary home-PN center. Clin Nutr 2017;36:812-7.

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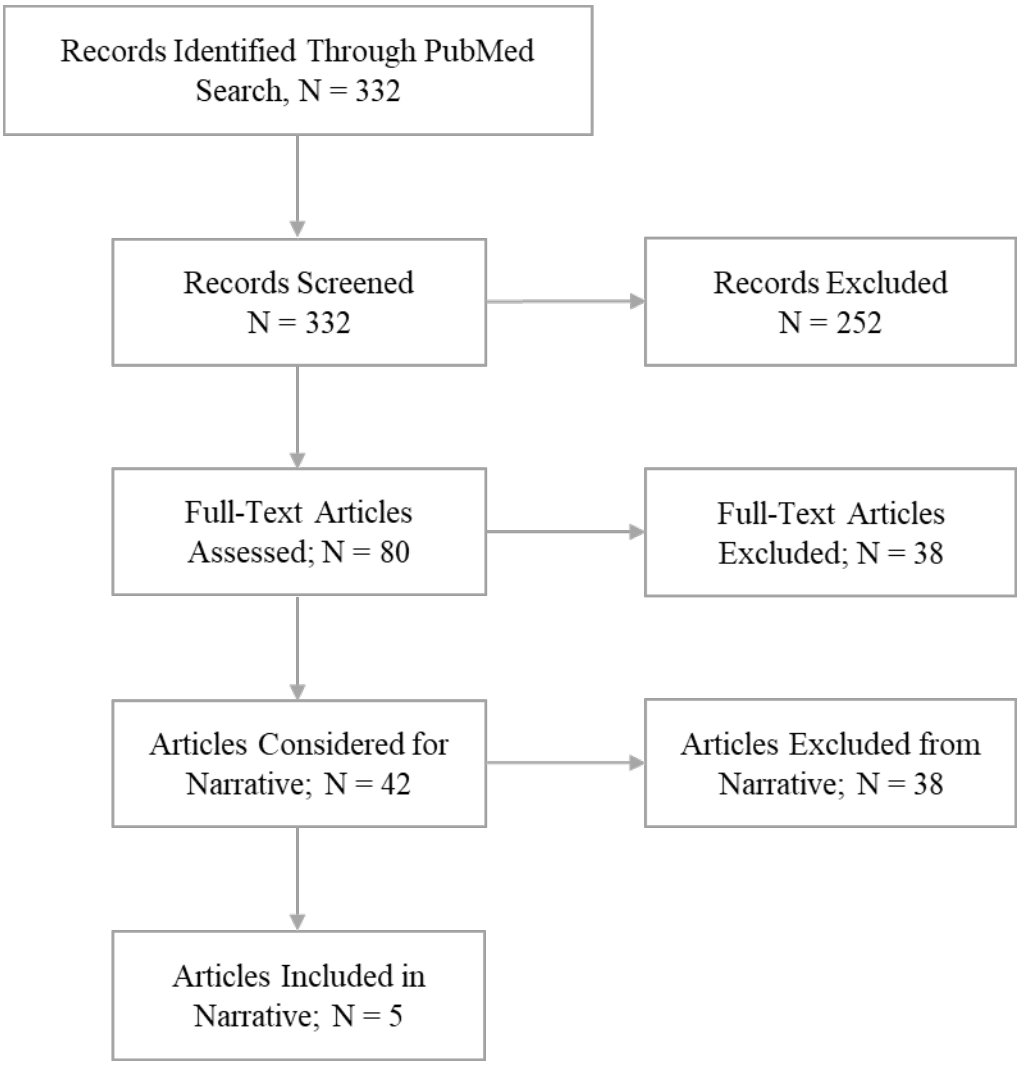
APPENDIX 1: DEPI supplemental literature search

On November 27, 2019, DEPI used (b) (4) query language, reproduced below, to update a (b) (4) PubMed search conducted on December 22, 2015. DEPI's search retrieved 332 PubMed records for articles published in 2015 or later.

(b) (4)

As summarized in Appendix Figure 1, a DEPI analyst (JLW) screened the titles and abstracts for these 332 PubMed records to select 80 articles for full-text examination. The full-text examination identified 42 full-text articles with results from original research (1) in patients given Cu parenterally or (2) about Cu status in patients on parenteral nutrition (**APPENDIX 2**). DEPI chose five articles for discussion in the review narrative [24,30,31,38,41].

Appendix Figure 1: PRISMA Flow Diagram



FOOTNOTE: See **APPENDIX 2** for lising of articles considered for narrative.

APPENDIX 2: Possibly informative articles identified by PubMed search

Bolded text identifies articles discussed by DEPI in the review narrative. Underlined text identifies additional articles discussed by the Sponsor in a Clinical Information Addendum submitted to NDA 209376 (eCTD 0017) on December 6, 2019.

1. Adler A, Worley S, Radhakrishnan K. Increased needs for copper in parenteral nutrition for children in the neonatal intensive care unit with an ostomy. Nutr Clin Pract 2019:10.1002/ncp.10365.

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pediatric patients with epilepsy. Epilepsia Open 2018;3:30-9.

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17. **Gupta K, Wang H, Amin SB. Copper supplementation in premature infants with parenteral nutrition-associated cholestasis. Nutr Clin Pract 2018;33:718-24.**

18. Hantaweepant C, Chinthammitr Y, Siritanaratkul N. Anemia and neutropenia in copper-deficient patients: A report of two cases and literature review. J Med Assoc Thai 2016;99:732-6.

19. Hortencio TDR, Arendt BM, Teterina A, et al. Changes in home parenteral nutrition practice based on the Canadian Home Parenteral Nutrition Patient Registry. JPEN J Parenter Enteral Nutr 2017;41:830-6.

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23. (b) (4)

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