

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209377Orig1s000**

**OTHER REVIEW(S)**

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

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

**Memorandum**

**Date:** July 11, 2019

**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 ZINC SULFATE INJECTION, for intravenous use

**NDA:** 209377

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In response to DGIEP's consult request dated October 29, 2018, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA submission for zinc sulfite.

**PI:** OPDP has no comments on the proposed labeling based on the draft PI received by electronic mail from DGIEP on July 5, 2019.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling received by electronic email from DGIEP on July 5, 2019, 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](mailto:meeta.patel@fda.hhs.gov).

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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MEETA N PATEL  
07/11/2019 11:16:06 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  
Office of Pharmacovigilance and Epidemiology**

**Pharmacovigilance Review**

**Date:** June 18, 2019

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DPV-I

**Product Name(s):** Zinc Sulfate Injection

**Subject:** Postmarketing Adverse Events

**Application Type:** NDA

**Submission Number:** 209377

**Applicant:** American Regent, Inc.

**OSE RCM #:** 2019-69

We would like to acknowledge and thank Dr. David Croteau for his contribution as a neurology consult on this review.

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## 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 Zinc Sulfate 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, the medical literature, and the Applicant's safety database to inform DGIEP as they conduct a priority review of a literature-based 505(b)2 New Drug Application (NDA) submitted by the Applicant of Zinc Sulfate Injection, American Regent, Inc.<sup>a</sup>

On October 12, 2018, a 505(b)2 NDA for Zinc Sulfate Injection was submitted to FDA. Zinc Sulfate Injection is proposed to be indicated as a source of the trace element zinc in parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. (b) (4)



We performed a hands-on review of the 18 adverse event reports submitted by the Applicant and none were deemed possibly or probably related to zinc for the following reasons: events were attributable to another concomitant medication or we were unable to exclude the role of other medications due to limited information, no individual patient was described in the report, the report did not contain an adverse event, or the report was unassessable due to limited information.

From our search of the FAERS database, we identified four cases that involved IV (n=1) and oral (n=3) Zinc Sulfate. The single case reported with IV Zinc Sulfate was related to a fatal 1000-fold overdose in an infant; the coroner listed cardiac failure caused by zinc intoxication as the cause of death. One of the cases with oral Zinc Sulfate reported the adverse event of pancytopenia in association with hypocupremia, which was also identified in multiple case reports published in the medical literature. The remaining two cases with oral Zinc Sulfate contained adverse events possibly attributable to the oral formulation itself (gastric ulcer perforation, drug-drug interaction with ciprofloxacin).

The CAERS database search retrieved three cases related to oral zinc supplementation (the specific zinc salts were not specified); however, the cases do not inform the labeling of IV Zinc Sulfate at this time due to the limitations of the cases and the products themselves. The allergic reactions described in two cases could be due to other components of the formulations given that some supplements have been known to contain undeclared ingredients. The remaining case, which did not contain all necessary information for assessment, described possible zinc toxicity with oral supplementation.

In the medical literature, we identified a subset of cases (n=30) describing medical complications (e.g., anemia, leukopenia, peripheral neuropathy) known to occur in the context of excess zinc-induced copper deficiency after long-term use. We also noted the association of zinc-induced

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<sup>a</sup> Original sponsor was Luitpold Pharmaceuticals, Inc.

hypocupremia with six cases of nephrotic-range proteinuria. Notably, most cases of hypocupremia described the use of oral zinc products (16/30), but 2 cases were related to chronic systemic administration of zinc (salt not specified) as a component of the dialysis solution in hemodialysis patients, suggesting that systemic administration of zinc can cause copper deficiency and related complications. It should also be noted that although anemia, leukopenia, and proteinuria are likely reversible after discontinuation of zinc and administration of copper, peripheral neuropathy was only partially reversible in some of the cases, thus magnifying the clinical significance of zinc-induced hypocupremia and resultant adverse events. (b) (4)

The medical literature search also identified four cases of hypersensitivity reactions with insulin-containing zinc preparations. The four cases of hypersensitivity occurred after treatment with zinc-containing insulin and all reported a lack of symptoms after administration of zinc-free insulin (or a reduced amount of zinc). Additionally, three of four cases reported additional testing to confirm a zinc allergy. These cases suggest that it may be possible to have an allergy to zinc, although this is a naturally occurring mineral that we consume in our diet. A general contraindication statement to avoid use in patients with known hypersensitivity to any component of the formulation should be added to the product label.

Lastly, the literature search identified two cases of seizure (b) (4) one case was deemed possible, although other etiologies could not be ruled out and the other case was unassessable.

In conclusion, our analysis of multiple data sources 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, we identified multiple adverse events (e.g., hypocupremia, hypersensitivity, overdose-related cardiac failure) reported with various zinc preparations (e.g., oral, parenteral, hemodialysis fluids, zinc-containing insulin), especially when used at high doses.

Based on this review, DPV-I recommends the following:

- Addition of case details from the preterm infant overdose case to the OVERDOSAGE section.
- (b) (4)
- Addition of a general contraindication statement to avoid use in patients with known hypersensitivity to any component of the formulation.
- Addition of hypocupremia and associated anemia, leukopenia, neutropenia, thrombocytopenia, myeloneuropathy, and nephrotic-range proteinuria to OVERDOSAGE.

# 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 Zinc Sulfate 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, the medical literature, and the Applicant's safety database to inform DGIEP as they conduct a priority review of a literature-based 505(b)2 New Drug Application (NDA) submitted by the Applicant of Zinc Sulfate Injection, American Regent, Inc.<sup>b</sup>

## 1.1 BACKGROUND<sup>c</sup> AND REGULATORY HISTORY

Parental nutrition (PN) is an intravenous (IV) administration of nutrition for patients who cannot maintain adequate intake via the oral and/or enteral routes. Patients may need PN for a variety of diseases or conditions that impair food intake, impair nutrient digestion or absorption (e.g., short bowel syndrome, gastrointestinal fistulas, bowel obstruction, severe acute pancreatitis), or increase nutritional requirements (e.g., critical illness). PN may be administered short-term or chronically, depending on a patient's unique nutritional needs. PN is referred to as total parenteral nutrition (TPN) when inclusive of protein (amino acids), carbohydrate (dextrose), fat (lipid emulsion), minerals and electrolytes, vitamins, and other trace elements (TEs), and is delivered via a central venous catheter.

TEs are minerals present at very low concentrations in humans. TEs are found in a variety of food 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.<sup>1</sup> Recommended Daily Allowances (RDAs)<sup>d</sup> or Adequate Intake (AI)<sup>e</sup> are used to determine the recommended daily oral intake of TEs in healthy individuals.<sup>2</sup>

Zinc is a TE which is integral for humans for the maintenance of enzyme systems, immune function, and protein synthesis. Zinc supports normal growth and is required for proper taste and smell. Zinc deficiency may result in growth retardation, sexual immaturity, loss of appetite, taste abnormalities, diarrhea, weight loss, alopecia, and impaired immune function. Additionally, zinc deficiency can be fatal in children with a rare genetic disorder called acrodermatitis enteropathica which prevents the intestine from absorbing zinc.<sup>3</sup>

Although zinc is an essential mineral, acute toxicity of high zinc intake may result in nausea, vomiting, diarrhea, and abdominal cramps. Chronic zinc toxicity, through inhibition of enteral copper absorption, can cause anemia, leukopenia, myeloneuropathy, and a decline in high-

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<sup>b</sup> Original sponsor was Luitpold Pharmaceuticals, Inc.

<sup>c</sup> Adapted from the backgrounder prepared for the Medical Policy & Program Review Council meeting on February 27, 2019, regarding TEs.

<sup>d</sup> 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.

<sup>e</sup> 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.

density lipoprotein cholesterol levels.<sup>4,5,6</sup> This mechanism of decreased copper absorption is utilized in the treatment of Wilson’s disease, which is a rare genetic disorder that results in copper build up in the body. The major manifestations of excess copper are neurologic disease and chronic liver disease leading to cirrhosis, which can be fatal.<sup>7</sup> Current recommended oral and parenteral doses for zinc are shown in Table 1 below.

<b>Population</b>	<b>Oral<sup>†</sup></b>	<b>Parenteral</b>
Adult <sup>2,9</sup>	11 mg (males) 8 mg (females) 11 mg (pregnant) 12 mg (lactating)	2.5-5 mg
Infants and Children <sup>2,10</sup>	2 mg (0-6 months) AI <sup>†</sup> 3 mg (7 months-3 years) 5 mg (4-8 years) 8 mg (9-13 years) 11 mg (males 14-18 years) 9 mg (females 14-18 years) 12 mg (<18 years pregnant) 13 mg (<18 years lactating)	450-500 mcg/kg (premature) 250 mcg/kg (infants < 3 months) 50 mcg/kg (infants > 3 months) 50 mcg/kg (children) <i>Max 5000 mcg/day</i>
Neonates <sup>2,10,11</sup>	1000-3000 mcg/kg (preterm) 2000 mcg (term)	400 mcg/kg (preterm) 250 mcg/kg (term)
* An individual patient may require higher doses (e.g., enterocutaneous fistulae, diarrhea, intestinal drainage, severe burns). † Enteral recommendations are the RDA unless one is not established, in which case the AI is listed and so noted in the table.		

Zinc Sulfate solution for injection is available in the United States as an unapproved product.<sup>f</sup> The available concentrations are Zinc Sulfate 1 mg/mL available in a 10 mL single dose vial (NDC Code 0517-6110-25) and 5 mg/mL available in a 5 mL vial (NDC Code 0517-8105-25).<sup>12</sup> It is also available as a component of an unapproved Multitrac-4 (MTE-4), MTE-4 Neonatal, MTE-4 Pediatric, MTE-4 Concentrate, Multitrac-5 (MTE-5) and MTE-5 Concentrate produced by American Regent.<sup>g</sup>

A 505(b)2 NDA for Zinc Sulfate Injection was filed by the Applicant, American Regent, Inc., on October 12, 2018, and this application is under priority review by FDA with a Prescription Drug User Fee Amendment (PDUFA) goal date of August 12, 2019. Zinc Sulfate Injection is proposed to be indicated as a source of the TE zinc in PN when oral or enteral nutrition is not possible, insufficient, or contraindicated. Each mL will provide either 3 mg (30 mg/10 mL) or 5 mg (25 mg/5 mL) of zinc.<sup>13</sup>

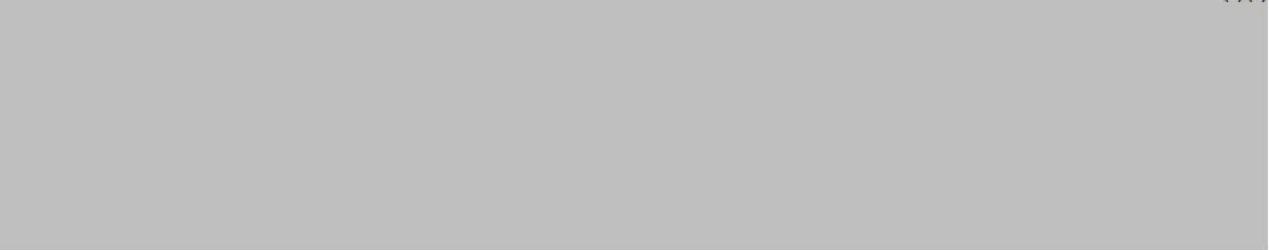
DGIEP consulted DPV-I on October 31, 2018, and January 24, 2019, to evaluate postmarketing adverse event reports in the FAERS database and medical literature with zinc supplementation to inform DGIEP as they review the ADVERSE REACTIONS (b) (4) section

<sup>f</sup> Zinc chloride solution for injection (NDA 018959 approved 6/26/86) is available through Hospira.

<sup>g</sup> MTE-4 contains zinc, copper, manganese, and chromium. MTE-5 contains zinc, copper, manganese, chromium, and selenium.

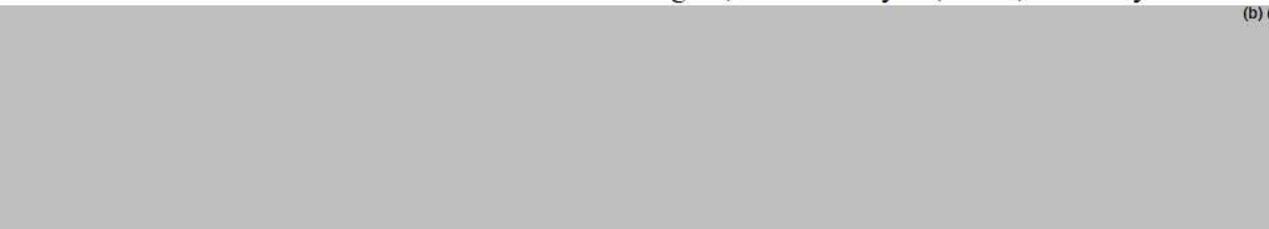
of the proposed product label submitted as part of the 505(b)2 NDA submission for Zinc Sulfate Injection.

DPV-I submitted an Information Request (IR) to American Regent, Inc. on January 30, 2019, to (b) (4)



On March 4, 2019, DPV-I and DGIEP discussed the possibility of using the CAERS database to evaluate adverse events reported with TE nutritional supplements, and it was determined that this evaluation would be included in the current review.

DGIEP and DPV-I submitted an IR to American Regent, Inc. on May 29, 2019, to clarify (b) (4)



## 1.2 PRODUCT LABELING

Select sections from the Applicant's proposed product label for NDA 209377 Zinc Sulfate Injection pertinent to this review are reproduced below.<sup>1,13</sup> Select sections from the Applicant's label for the unapproved Zinc Sulfate solution for injection (NDC Code 0517-8105-25 and 0517-6110-25),<sup>12</sup> updated December 19, 2018, are in Appendix A.

### 5 WARNINGS AND PRECAUTIONS

(b) (4)  


#### 5.3

This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. (b) (4) patients with impaired kidney function 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.

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 (b) (4)

(b)  
(4)

6 ADVERSE REACTIONS

(b) (4)



## 10 OVERDOSAGE

## 2 METHODS AND MATERIALS

### 2.1 CAUSALITY ASSESSMENT

Reports were assessed for a causal relationship between the adverse events and zinc 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.

<b>Table 2. Causality Classification and Criteria based on the WHO-UMC System<sup>16</sup></b>	
Causality Term	Assessment Criteria
Certain	<ul style="list-style-type: none"> <li>• Event or laboratory test abnormality, with plausible time relationship to drug intake</li> <li>• Cannot be explained by disease or other drugs</li> <li>• Response to withdrawal plausible (pharmacologically, pathologically)</li> <li>• Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon)</li> <li>• Rechallenge satisfactory, if necessary</li> </ul>
Probable/Likely	<ul style="list-style-type: none"> <li>• Event or laboratory test abnormality, with reasonable time relationship to drug intake</li> <li>• Unlikely to be attributed to disease or other drugs</li> <li>• Response to withdrawal clinically reasonable</li> <li>• Rechallenge not required</li> </ul>
Possible	<ul style="list-style-type: none"> <li>• Event or laboratory test abnormality, with reasonable time relationship to drug intake</li> <li>• Could also be explained by disease or other drugs</li> <li>• Information on drug withdrawal may be lacking or unclear</li> </ul>

<b>Table 2. Causality Classification and Criteria based on the WHO-UMC System<sup>16</sup></b>	
Unlikely	<ul style="list-style-type: none"> <li>• Event or laboratory test abnormality, with a time to drug intake that makes relationship improbable (but not impossible)</li> <li>• Disease or other drugs provide plausible explanations</li> </ul>
Unassessable	<ul style="list-style-type: none"> <li>• Report suggesting an adverse reaction</li> <li>• Cannot be judged because information is insufficient or contradictory</li> <li>• Data cannot be supplemented or verified</li> </ul>

## 2.2 APPLICANT’S SEARCH STRATEGY

The Applicant included all reports with Zinc Sulfate, MTE-4, or MTE-5 reported to the Applicant’s Pharmacovigilance unit as a suspect or concomitant medication.<sup>k</sup>

## 2.3 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in Table 3.<sup>1</sup>

<b>Table 3. FAERS Search Strategy*</b>	
Date of Search	May 2, 2019
Time Period of Search	All reports through May 1, 2019
Search Type	Quick Query
Product Terms	Product Active Ingredient (PAI): zinc sulfate heptahydrate; zinc sulfate monohydrate; zinc sulfate, unspecified form; zinc sulfate\zinc sulfate anhydrous
* See Appendix B for a description of the FAERS database.	

## 2.4 CAERS SEARCH STRATEGY

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

<b>Table 4. CAERS Search Strategy</b>	
Date of Search	May 6, 2019
Time Period of Search	All reports through May 5, 2019
Search Type	PRIMO
Product Terms	Product Name contains: “zinc”
* See Appendix B for a description of the CAERS database.	

<sup>k</sup> MTE-4 contains zinc, copper, manganese, and chromium. MTE-5 contains zinc, copper, manganese, chromium, and selenium.

<sup>1</sup> We conducted a FAERS search on March 4, 2019, for adverse events reported with all zinc salts. The search retrieved 4561 reports, of which 4080 involved formulations not pertinent to this review (e.g., sunscreen, diaper rash cream, foot powder, nasal gel). We reviewed a sample of the remaining reports, including reports noting “TPN” or “parenteral nutrition,” and did not identify any relevant cases. Therefore, we refined our search as described in Table 3.

## 2.5 LITERATURE SEARCH STRATEGY

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

Date of Search	May 31, 2019
Database	Embase, PubMed@FDA, Google Scholar
Search Terms	Embase Search 1: (Zinc) AND (Adverse Drug Reaction) OR Toxicity; Embase Search 2: (Zinc) AND (Case Report)  PubMed Search 1: (Zinc) AND (Adverse Drug Reaction OR Toxicity); PubMed Search 2: (Zinc) AND (Case Report)  Google Scholar Search 1: (Zinc) AND (Adverse Drug Reaction OR Toxicity); Google Scholar Search 2: (Zinc) AND (Case Report)
Years Included in Search	All
* A targeted search of the references was also completed to identify additional case reports.	

## 3 RESULTS

### 3.1 APPLICANT'S DATABASE RESULTS

The Applicant's search retrieved 18 reports of adverse events with Zinc Sulfate Injection, MTE-4 Concentrate, MTE-4 Pediatric, MTE-5, or MTE-5 Concentrate. Of the 18 reports, 4 reported Zinc Sulfate Concentrate as a suspect (n=2) or Zinc Sulfate as a concomitant product (n=2). The remaining 14 reports listed MTE-4 Concentrate (n=1), MTE-4 pediatric (n=1), MTE-5 (n=10), and MTE-5 Concentrate (n=3) as a suspect product.<sup>m</sup> See Appendix C for a line listing of reports retrieved by the Applicant.

The two reports that listed Zinc Sulfate Concentrate injection as a suspect product described a husband and wife who experienced similar adverse events (e.g., sweating, lethargy, muscle rigidity, loss of consciousness) shortly after receiving a Meyer's cocktail infusion<sup>n</sup> for stress management at a naturopathic clinic; the Meyer's cocktail contained selenium, concentrated Zinc Sulfate Injection, and "other unknown components." Both reports that listed Zinc Sulfate Injection as a concomitant product described adverse events attributed to calcium gluconate contaminated with bacterial endotoxin.

Of the 14 reports with MTE, 2 reports described an allergic reaction assessed by the Applicant to be invalid as there was no identifiable patient, 2 reports did not describe an adverse event, and 2 reports were unassessable. Five reports described adverse events attributed to calcium gluconate

<sup>m</sup> MTE-5 and MTE-5 Concentrate were reported as co-suspects in one report describing a concentration error.

<sup>n</sup> The physician noticed the IV was running a little fast and went to slow it down when she noticed the patients' reactions.

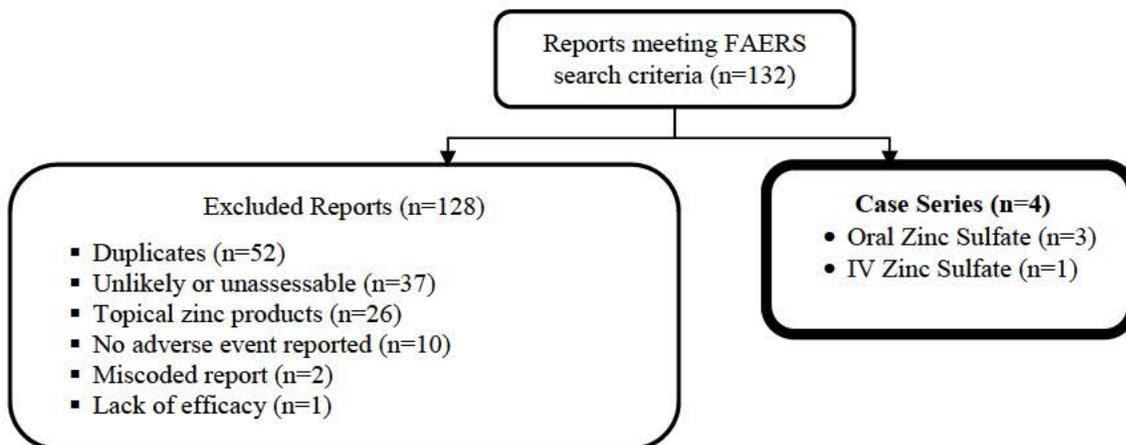
contaminated with bacterial endotoxin. One report described a medication concentration error resulting in burning at the infusion site after IV administration of 3 mL of MTE-5 (dilution not provided); burning resolved upon discontinuation. One report described increased chromium levels with MTE-4 Concentrate, which contains chromium. The remaining report described lithium toxicity, hypokalemia, and severe hypoglycemia in a 31-week-old infant on TPN attributed to MTE-4 Pediatric and calcium gluconate contaminated with lithium.

*Reviewer's comment: Based on our hands-on review, none of the Applicant's reports were deemed possibly or probably related to Zinc Sulfate Injection for the following reasons: events were attributable to another concomitant medication or we were unable to exclude the role of other medications due to limited information, no individual patient was described in the report, the report did not contain an adverse event, or the case was unassessable due to limited information.*

### 3.2 FAERS DATABASE RESULTS

The FAERS search of Zinc Sulfate products retrieved 132 reports. After accounting for 52 duplicate reports from the Applicant's database search<sup>o</sup> (n=2) and within FAERS (n=50), 80 reports were analyzed for inclusion in the case series of adverse events reported with Zinc Sulfate use. Four reports were included in the case series (see Figure 1 for details of the FAERS case selection). See Appendix D for a line listing of reports retrieved in FAERS.

**Figure 1. FAERS Case Selection for Zinc Sulfate products**



The four cases in the FAERS case series reported the following adverse events: accidental overdose leading to cardiac failure and death (IV formulation), zinc toxicity leading to copper deficiency resulting in pancytopenia, gastric ulcer perforation, and drug interaction with ciprofloxacin. These cases are further discussed below.

<sup>o</sup> Two FAERS reports were excluded as they were previously evaluated from the cases submitted by the Applicant. The remaining 16 cases submitted by the Applicant were not retrieved in the FAERS search because the FAERS search strategy did not include MTE-4, MTE-5, or Zinc Sulfate as a concomitant product only.

**FAERS Case #16198491, outcome: death, USA, 2019:**

A literature case report<sup>17</sup> described a preterm female infant born at 26 weeks gestation that was prescribed TPN on the day of birth. The physician ordered zinc 330 mcg/100 mL to be added to the TPN. The pharmacist converted to a mcg/kg dose and entered into the computer in mg, rather than mcg, resulting in a 330 mg/100 mL concentration. Another pharmacist checked the work and did not notice the erroneous change. The pharmacy technician that prepared the TPN replenished the compounder syringe containing zinc 11 times while preparing the solution, requiring dozens of vials of zinc sulfate. A third pharmacist checked the TPN additives prior to adding them to the solution and did not catch the error. Approximately three hours after the bag was hung, the error was discovered, and the pharmacist immediately called the unit to stop the infusion. The infant received edetate calcium disodium compounded by an external pharmacy. The chelation therapy was unsuccessful, and the infant died. The coroner listed cardiac failure caused by zinc intoxication as the cause of death.

*Reviewer's comment: This case was considered possible based on the temporal relationship. No additional clinical details regarding the events leading up to the fatal cardiac failure were reported.*

**FAERS Case #10252595, outcome: other serious outcome, USA, 2014:**

A literature case report<sup>18</sup> described a 15-year-old female with a past medical history of myelodysplastic syndrome, Ewing's sarcoma, bone marrow transplant, thrombocytopenia, idiopathic pneumonia syndrome, graft versus host disease in skin, zinc deficiency, and chromosomal abnormality not otherwise specified. Concomitant medications included acyclovir, cetirizine, sulfamethoxazole-trimethoprim, ergocalciferol, etanercept, hydrocortisone, lansoprazole, methotrexate, morphine, mycophenolate mofetil, ondansetron, pentamidine, potassium chloride, sertraline, and zolpidem. The patient underwent bone marrow transplant (BMT). Two days prior, she received cyclosporine as prophylaxis for graft-versus-host disease. On day 95 after the BMT, she developed microangiopathic hemolytic anemia, thus cyclosporin therapy was changed to mycophenolate mofetil. On day 154 after the BMT, tests revealed a low zinc level, and she was treated with oral Zinc Sulfate 200 mg/day for two weeks. On day 168 after the BMT, tests revealed a normal zinc level, and she was instructed to discontinue the zinc therapy. On day 336 after the BMT, she developed thrombocytopenia and was noted to have anemia requiring transfusion. On day 399 after the BMT, she developed pancytopenia. Her bone marrow aspirate revealed a hypocellular marrow with trilineage haematopoiesis and mild erythroid dysplasia. Two months later she developed neutropenia. On day 454 after the BMT, the pancytopenia worsened. Repeat bone marrow aspirate and biopsy results were consistent with the previous findings. A cytoplasmic vacuolization was noted in the myeloid and erythroid precursor cells. Analysis revealed an elevated zinc level and low copper level. The family admitted to continuing the zinc supplement due to the benefits on the immune system. The Zinc Sulfate therapy was discontinued, and the patient was treated with copper supplements. Within one month, her complete blood counts, zinc levels, and copper levels had normalized. She remained in remission four years after the BMT.

*Reviewer's comment: This case described chronic zinc toxicity and copper deficiency with pancytopenia, which were probably caused by high dose (200 mg/day) oral Zinc Sulfate supplementation (recommended oral Zinc Sulfate daily dose for a 15-year-old female is 9 mg per*

Table 1). Presence of cytoplasmic vacuolization of the myeloid and erythroid precursor cells in the bone marrow is highly suggestive of zinc-induced copper deficiency.<sup>19</sup> Decreased intestinal copper absorption is a well-documented adverse event associated with chronic high doses of oral zinc supplementation (b) (4)

. Hypocupremia results from increased synthesis of metallothionein in the intestinal epithelial cells induced by zinc, which binds copper<sup>p</sup> and prevents its absorption.<sup>20,21</sup>

**FAERS Case #12227031, outcome: hospitalization, other serious outcome, France, 2016:**

A literature case report<sup>22</sup> described a 24-year-old female with a past medical history of Wilson's disease taking Zinc Sulfate 200 mg three times daily for more than 5 months. The patient also took two diclofenac over the last day for dorsalgia. The patient was seen in the emergency room (ER) for acute epigastric pain. An emergent laparoscopic exploration confirmed a perforated gastric ulcer. The perforation was subsequently closed, and postoperative antibiotics and high-dose IV proton pump inhibitors were initiated. Neither malignancy nor *Helicobacter pylori* infection were found. Zinc Sulfate was switched to Trientine<sup>q</sup> 300 mg three times daily.

*Reviewer's comment: This case reported occurrence of a gastric ulcer perforation possibly caused by high doses of oral Zinc Sulfate<sup>r</sup> for 5 months. Despite limited baseline information in the case, no underlying risks of perforation were noted other than the patient taking two diclofenac. Gastric irritation is labeled for oral zinc supplementation,<sup>23</sup> and the supplementation cannot be excluded as a contributor to the development of the gastric ulcer and subsequent perforation.<sup>24</sup> This event may be specific to the oral formulation, however, the limited data in this case and lack of other cases of this adverse event precludes a full assessment of this safety issue.*

**FAERS Case #9508074, outcome: hospitalization, other serious outcome, Great Britain, 2013:**

A pharmacist reported that a 75-year-old female received ciprofloxacin 500 mg twice daily for a lower respiratory tract infection with *Staphylococcus aureus* present in a sputum sample. The patient was taking Zinc Sulfate, calcium carbonate, and cholecalciferol daily; no other concomitant medications were reported. The patient was later admitted (unknown date) with an unresolved infection, increased shortness of breath, and acute kidney injury. Treatment with ciprofloxacin was discontinued six days after initiation due to treatment failure, which was suspected to be from the interaction with calcium and zinc. The patient had a past medical history of chronic obstructive pulmonary disease, hypertension, ischemic heart disease, polymyalgia rheumatica, and rheumatoid arthritis.

*Reviewer's comment: This case described possible antibiotic treatment failure from a drug-drug interaction between ciprofloxacin and the multivalent cations, calcium and zinc. The interaction*

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<sup>p</sup> Metallothionein binds zinc, copper, and cadmium. Copper has a higher affinity for binding metallothionein leading to displacement of zinc and reduced copper absorption.

<sup>q</sup> Trientine is a copper chelator.

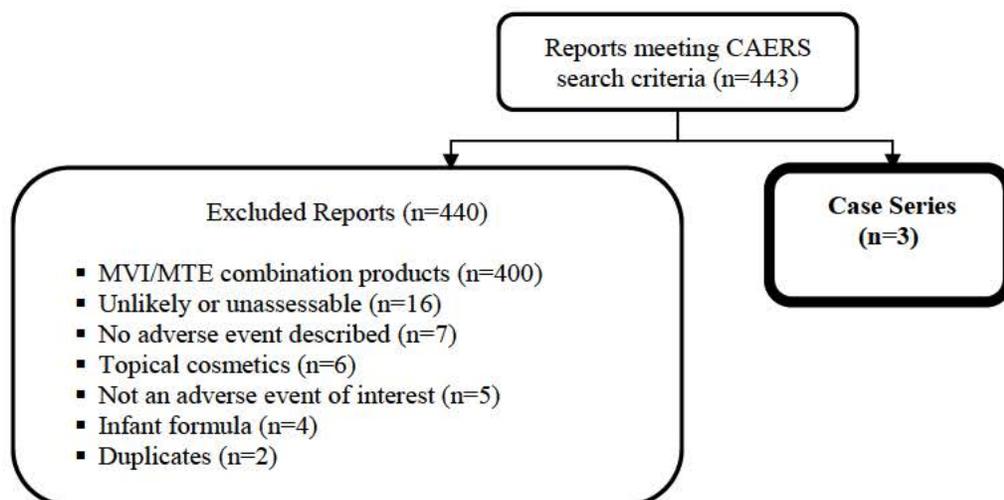
<sup>r</sup> Zinc Acetate is recommended at a starting dose of 25 to 50 mg of elemental zinc three times daily in adults with Wilson disease. Zinc Sulfate contains 23% elemental zinc; Zinc Sulfate at a dose of 200 mg three times daily (600 mg) daily is equivalent to 138 mg elemental zinc.

with multivalent cations is labeled in *DOSAGE AND ADMINISTRATION Important Administration Instructions of the ciprofloxacin product label*.<sup>25</sup> Specifically, the label instructs patients to administer ciprofloxacin at least 2 hours before or 6 hours after products containing calcium, iron, or zinc due to decreased absorption. This interaction is specific to the oral formulation.

### 3.3 CAERS DATABASE RESULTS

The CAERS search retrieved 443 reports, which contained 2 duplicates. Of the 441 unique reports, 410 were excluded from hands-on review because zinc was a component of an MVI/MTE combination product (n=400), a topical cosmetic (n=6), or an infant formula (n=4). The remaining 31 reports were included in the hands-on review to evaluate for adverse events reported with oral zinc supplementation (see Figure 2 for details of the CAERS case selection). See Appendix E for a line listing of reports retrieved in CAERS.

**Figure 2. CAERS Case Selection**



The three cases in the CAERS case series reported the adverse events of hypersensitivity (n=2; rash, rash and shortness of breath) and zinc overdose (n=1). These cases are further discussed below.

#### **Case #137269, outcome: other serious outcome, USA, 2011:**

The mother of a 39-year-old female with multiple sclerosis reported her daughter started using zinc 50 mg caplets orally daily for immune health. On the second day after initiation, 12 hours after taking the product, the daughter developed a red itchy rash on her palms, arms, chest, and legs. She was taken to the ER and was treated with IV prednisone and diphenhydramine. The rash improved the same day. The mother reported the ER physician diagnosed her daughter with an allergic reaction but was unsure of what caused the reaction. The daughter was also taking natalizumab, but the zinc was reported to be the only new product introduced to her. A quality investigation was initiated, and all ingredients were found to be at analytically acceptable levels without quality issues noted. The batch record found no contributing factors noted to cause an allergic reaction.

**Case #146222, outcome: other serious outcome, USA, 2011:**

A 19-year-old female with a past medical history of asthma and allergies without concomitant medications reported she started GNC zinc 100 mg orally daily. On the second day after initiation, 30 minutes after taking the second dose of the product, she developed a rash and shortness of breath. She discontinued the product and took diphenhydramine, and the events resolved later that day (no medical evaluation was performed).

*Reviewer's comment: The two CAERS cases described above reported allergic reactions possibly caused by ingestion of different oral zinc supplements. The time to event is suggestive of a causal role of the zinc product, but it is important to note either excipients or undeclared active ingredients that may be present in unregulated supplements could be allergenic and the cause of these adverse events.<sup>26</sup> Our causality assessment to the zinc component of the tablet is limited by lack of information on the latter variables.*

**Case #158709, outcome: other serious outcome, USA, 2012:**

A 45-year-old female with a past medical history of high blood pressure initiated GNC zinc 100 mg. She was also taking metoprolol extended release 50 mg daily, triamterene 37.5 as needed, MSG 1000 mg, echinacea, vitamin D 1000, and calcium carbonate. The patient reported that after taking the first dose of zinc, she felt “sick to the stomach” with nausea, feeling a little hot, and wanting to throw up. On the second day after initiation, she took the product without her other vitamins, which she had been taking for more than a year and experienced the same symptoms. On the third day after initiation, she took a half tablet and did not experience any symptoms. Nine months later, she took a whole tablet and reported feeling hot, sweating, severe stomach cramps, and vomiting. She was taken to the ER by ambulance, diagnosed with zinc overdose and dehydration, and treated with IV fluids. All symptoms except stomach cramping resolved in the ER. She was discharged the same day and instructed to discontinue all vitamins and follow up with her physician. Six days following discharge, stomach cramps continued with food.

*Reviewer's comment: This patient experienced recurrent adverse events (such as nausea, feeling hot, vomiting) after taking zinc 100 mg on multiple occasions. The adverse events did not occur when the patient reduced the dose of zinc sulfate to 50 mg once. No supporting details of zinc toxicity were provided. It is unclear if the symptoms described in this case are related to zinc toxicity based on the timing of development (after the first dose) or common gastrointestinal adverse reactions related to the oral formulation.*

### **3.4 LITERATURE SEARCH**

The literature search did not identify additional cases of adverse events associated with standard recommended doses of zinc. However, the search identified 37 cases<sup>s</sup> from 32 publications relevant to this review. Of the 37 cases, 30 reported anemia, leukopenia, thrombocytopenia, neuropathy, and/or nephropathy in association with hypocupremia from excessive doses of zinc; an additional case reported anemia and leukopenia but did not measure the patient's copper level

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<sup>s</sup> Porter et al reported a case of hypocupremia with normal zinc blood levels. Broun et al reported a case of zinc toxicity with associated anemia and leukopenia; serum copper levels were not obtained.

at the time of the event. Four cases described hypersensitivity reactions related to zinc in insulin preparations and the remaining two cases reported seizures in a patient with a high zinc level and a patient receiving an excess dose of zinc (see Appendix F for case references and additional case details).

### Hypocupremia (n=30)

We retrieved 27 papers published between 1978 and 2019 reporting 30 cases of normal (n=1)<sup>27</sup> or high (n=29) zinc blood levels and hypocupremia following exposure to excessive amounts of zinc. Of the 30 cases, 16 involved oral zinc products, 4 involved ingestion of zinc-containing denture paste, 2 reported administration of parenteral zinc in hemodialysis fluid, 2 involved intake of zinc-containing coins, and 6 had an unknown source of zinc exposure. Twelve of 16 cases that involved oral zinc reported the zinc product: Zinc Sulfate (n=6), Zinc Gluconate (n=3), polaprezinc (n=1), Zinc Acetate (n=1), and Zinc Amino Acid Chelate (n=1). The median daily dose of elemental zinc reported in the cases involving oral products (n=10) was 140 mg/day, ranging from 30 to 307 mg/day. Neither case that involved parenteral zinc reported the specific product involved in the event. The median time to onset for the development of hypocupremia (n=19) was 42 months (3.5 years), ranging from 10 to 264 months (22 years).<sup>†</sup>

The signs and symptoms associated with zinc-induced hypocupremia varied in the cases, including anemia (n=26), leukopenia (n=22<sup>‡</sup>), sensory-motor peripheral neuropathy with gait ataxia (n=18), nephrotic range proteinuria (n=6), thrombocytopenia (n=2), and pancytopenia (n=1).<sup>§</sup> Of the 30 cases, 29 received treatment for the events (discontinuation of zinc n=19, copper supplementation n=19, coin removal n=2) and 1 did not report treatment. Anemia, leukopenia, or neutropenia improved or recovered completely after treatment in most cases (20/28); 7 did not report the response to treatment and 1 worsened after discontinuation of zinc and initiation of a high copper diet. After treatment the peripheral neuropathy was reported as partially improved (n=8), unchanged (n=5), resolved (n=2), stabilized (n=1), or worsened (n=1); the remaining case did not report the response to treatment. The poor response of the peripheral neuropathy to treatment can be explained by presence of structural damage of the spinal cord in 14 of 15 cases that underwent spinal magnetic resonance imaging and by abnormal nerve conduction studies and/or electromyography in 11 cases.<sup>¶</sup>

Six of 30 cases reported nephrotic-range proteinuria (median: 8.85 g; range: 3.8-24 g);<sup>‡</sup> one case also reported HCV infection as possible alternative etiology for the development of the nephrotic range proteinuria and the remaining 5 did not report information to rule out common causes. A kidney biopsy identified the following underlying renal lesions in five of the six cases: minimal

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<sup>†</sup> The median time to onset for the development of hypocupremia in the cases involving oral zinc (n=15) was 24 months, ranging from 10 to 264 months (22 years). The two cases involving zinc administration via hemodialysis occurred after 6 years and 10 years.

<sup>‡</sup> Of the 22 cases of leukopenia, 15 also noted neutropenia.

<sup>§</sup> A case may report more than one adverse event.

<sup>¶</sup> Of the hypocupremia cases that reported time to improvement in hematologic values, the median was 21 days (range: 7-90 days, n=18); improvement in neuropathy symptoms, the median was 42 days (range: 14-180 days, n=6); improvement in proteinuria, the median was 168 days (35 days and 300 days, n=2); improvement in copper/ceruloplasmin levels, the median was 49 days (range: 21-90 days, n=3).

<sup>x</sup> A nephrologist medical officer in DPV reviewed the renal cases.

change disease (n=2), membranoproliferative glomerulonephritis (n=2), and focal segmental glomerulosclerosis (n=1). The proteinuria improved substantially in all cases (median proteinuria: 1.05 g/day; range: 0.02-3.1 g/day) after discontinuation of zinc (n=6) and institution of copper replacement (n=2).

*Reviewer comment: These cases confirm medical complications known to occur because of chronic zinc toxicity, including suppression of all bone marrow cell lines and development of a peripheral myeloneuropathy. More noteworthy is the observation that although the marrow suppression was mostly reversible after discontinuation of zinc and copper supplementation, the peripheral myeloneuropathy had a poor prognosis with only partial or no recovery in most cases. In addition, 6 of 30 cases presented with nephrotic-range proteinuria, which improved substantially but did not resolve completely after discontinuation of zinc and copper supplementation. Considering that nephrotic-range proteinuria occurs very rarely in individuals that do not suffer from diabetes mellitus, hepatitis virus infection, cancer, or collagen-vascular disease, its presence in >20% of these reports is difficult to attribute merely to chance.*

#### Hypersensitivity (n=4)

A single literature article published in 1979 reported two cases of pruritic, indurated lesions after injection of zinc-containing insulin. The first case described a 64-year-old male who developed pruritic, erythematous, papular injection-site lesions 24 hours after administration of NPH insulin<sup>y</sup> which contained zinc; no improvement occurred after subsequent trials of four different zinc-containing insulin preparations (NPH beef, lente, regular, single-component), but symptom resolution was noted after switching to zinc-free insulin. The second case described a 48-year-old woman with similar symptoms to the first case with use of longer-acting insulin; she was able to receive regular pork insulin after desensitization (the authors noted that this preparation had a lower zinc content than longer-acting insulin), and zinc-free insulin caused her “no ill-effects.” Subsequent testing (intradermal skin testing, lymphocyte studies) confirmed the zinc allergy in both patients.

A foreign literature article published in 1985 reported that a 61-year-old male with diabetes for 21 years and a history of intermittent treatment with various insulin preparations developed an immediate generalized cutaneous allergy of urticaria when changed from Actrapid MC (the diluting medium contains no zinc) to Monotard MC (porcine monocomponent insulin). The same reaction was observed after treatment with Monotard HM (human semisynthetic monocomponent insulin). After switching to Actrapid HM (human semisynthetic monocomponent insulin), the patient was free from allergic manifestations. Skin intradermal tests were negative to bovine, porcine, and human insulin, but strongly positive to zinc acetate and the diluting medium for Monotard (contains ~50 mcg of zinc/mL). The authors commented that Monotard MC and HM contain high amounts of zinc (~85 mcg /mL), whereas Actrapid MC and HM contain low amounts of zinc (5-8 mcg zinc/mL).

Another foreign literature article published in 2010 reported that a 61-year-old male patient experienced induration at the injection site, swelling, erythema, and intense pruritis 1 hour after receiving NPH insulin. The symptoms evolved to generalized urticaria with face edema and

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<sup>y</sup> U.S. product labeling for Humulin N (human insulin [rDNA origin] isophane suspension) last revised 11/2018 contains the inactive ingredient of zinc oxide adjusted to provide 0.025 mg zinc ion.

dyspnea and regressed after a few hours. The same manifestations occurred with a second dose and resolved with corticoid treatment. The patient experienced the same manifestations after being switched to Actrapid insulin; he was then switched back to oral anti-diabetics. A few years later, he was trialed on Levemir insulin (detemir)<sup>z</sup> and had the same allergic manifestations. The patient was subsequently assessed for an insulin allergy by skin prick test; only zinc chloride displayed positive results after approximately 10 minutes, and a second prick test using 20- and 40-fold dilutions of zinc chloride were both positive. The patient was then treated with glulisine<sup>aa</sup>, a zinc-free insulin, and never experienced an allergic reaction during 8 months of treatment.

*Reviewer comment: The presence of multiple cases reporting the occurrence of a hypersensitivity event to a zinc-containing insulin and lack of symptoms after administration of zinc-free (or a reduced amount of zinc) insulin, strong temporal association within the cases, and reasonable investigation to rule out alternative etiologies suggests a probable causal association between the zinc component and the hypersensitivity events. Although rare, an allergy to insulin or other components of some insulin preparations such as protamine is possible, however, the cases provide reasonable evidence to exclude these allergens as a cause of the events.*

#### Seizure (n=2)

A foreign case from 1982 reported that a premature infant with characteristic skin lesions of secondary acrodermatitis along with failure to thrive and diarrhea was initiated on Zinc Sulfate 3 mg/kg of body weight (body weight and route of administration not reported) and experienced accidental zinc intoxication (zinc level 34.4 micromoles/liter; normal 12-20 micromoles/liter) manifested as irritability, tremor, seizures, mydriasis, and tachycardia.

A second foreign case from 2008 reported a 28-year-old male with a 16-year history of seizures self-administered Zinc Gluconate 240 mg orally twice daily (64 mg of elemental zinc per day) for 2 days and experienced 6 complex partial seizures in 1 day, with 2 of the seizures generalizing to tonic-clonic convulsions, followed by 3 complex partial seizures the next day. He discontinued the zinc and had no further seizures, but he reinitiated zinc 1 month later and had increased seizure recurrence (7 seizures over 3 days). The patient had been receiving phenytoin 300 mg daily for his seizures, and his seizures typically commenced with an epigastric “rising sensation”, followed by unconscious staring spells lasting 1-2 minutes, which sometimes generalized to tonic-clonic convulsions.

*Neurologist Medical Officer comment: The first case was deemed to be unassessable; we do note that the dose of zinc reported in the case to be within the recommended dosing range for oral Zinc Sulfate for a preterm neonate per Table 1.*

*The second case was deemed to be possible. Although there was supportive chronological data (given short latency and positive rechallenge with similar latency), case level biological plausibility (for higher than recommended zinc dose), good report information quality, and a*

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<sup>z</sup> U.S. product labeling for Levemir (insulin detemir injection) last revised 1/2019 contains the inactive ingredient of 65.4 mcg of zinc.

<sup>aa</sup> U.S. product labeling for Apidra (insulin glulisine injection) last revised 12/2018 does not contain zinc as an inactive ingredient.

*reasonable investigation into alternative etiologies, other etiologies are possible (e.g., individual susceptibility or unrecognized concurrent factors with a contributory role).*

#### **4 DISCUSSION**

We searched the FAERS database, the CAERS database, the medical literature, and reviewed the results from the Applicant's safety database search and 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, we identified multiple adverse events (e.g., hypocupremia, hypersensitivity, overdosage-related cardiac failure) reported with various zinc preparations (e.g., oral, parenteral, hemodialysis fluids, zinc-containing insulin), especially when used at high doses.

After review of postmarketing reports of adverse events with oral and injectable zinc supplementation in the Applicant's database, no cases were found to be possibly or probably related to zinc. (b) (4)

(b) (4)



From our search of the FAERS database, we identified four cases that involved IV (n=1) and oral (n=3) Zinc Sulfate. The single case reported with IV Zinc Sulfate was related to a fatal 1000-fold overdose in an infant; the coroner listed cardiac failure caused by zinc intoxication as the cause of death. One of the cases with oral Zinc Sulfate reported the adverse event of pancytopenia in association with hypocupremia, which was also identified in multiple case reports published in the medical literature; this patient received a dose of oral Zinc Sulfate approximately 22 times the age recommended dose for females (received 200 mg/day, recommended dose is 9 mg/day). The remaining two cases with oral Zinc Sulfate contained adverse events possibly attributable to the oral formulation itself (gastric ulcer perforation, drug-drug interaction with ciprofloxacin).

The CAERS database search retrieved three cases related to oral zinc supplementation (the specific zinc salts were not specified); however, the cases do not inform the labeling of IV Zinc Sulfate at this time due to the limitations of the cases and the products themselves. The allergic reactions described in two cases could be due to other components of the formulations given that some supplements have been known to contain undeclared ingredients. The remaining case, which did not contain all necessary information for assessment, described possible zinc toxicity with oral supplementation.

In the medical literature, we identified a subset of cases (n=30) describing medical complications (e.g., anemia, leukopenia, peripheral neuropathy, nephrotic-range proteinuria) that occurred in the context of copper deficiency after long-term use of excess zinc. Zinc cation, regardless of the ligand, blocks the intestinal absorption of copper from the diet and the reabsorption of endogenously secreted copper such as that from the saliva, gastric juice, and bile. Zinc induces

the production of metallothionein in the enterocyte, a protein that binds copper thereby presenting its serosal transfer into the blood; it is also postulated that zinc can induce metallothionein in the liver. The bound copper is then lost in the stool following desquamation of the intestinal cells.<sup>21,28</sup> This mechanism of copper excretion is utilized in patients with Wilson disease, an autosomal recessive metabolic defect in hepatic excretion of copper in the bile, resulting in accumulation of excess copper in organs such as the liver, brain, and kidneys.

On May 31, 2019, in an IR response, the Applicant stated that the drug interaction for zinc and copper pertained to oral zinc administration taken over extended periods of time only. The Applicant did not find any studies identifying clinically-relevant drug interactions between IV zinc and copper. Although we agree that most cases of hypocupremia occurred with oral zinc products (16/30 involved oral zinc in our medical literature results) and over extended periods of time (median time to onset was 2 years in the medical literature cases), we do not agree with the Applicant's assertion that IV zinc products cannot cause the same interaction.<sup>15</sup> Notably, two medical literature cases were related to chronic systemic administration of zinc (salt not specified) as a component of the dialysis solution in hemodialysis patients, suggesting that systemic administration of zinc can cause copper deficiency and related complications.<sup>29,30</sup>

There may be multiple reasons for a lack of cases of hypocupremia when zinc is administered IV as part of PN solution. Copper may be administered concomitantly in PN solution. Additionally, the doses of elemental zinc reported in the medical literature cases were above the equivalent recommended doses for supplementation in PN. It is important to note that 25 mg three times daily of oral elemental zinc (in the form of Zinc Acetate) is the lower range of the recommended starting dose for treatment of Wilson disease. After taking into account oral bioavailability (~30%<sup>31</sup>), the total daily dose would be comparable to approximately 98 mg of IV Zinc Sulfate (23% elemental zinc<sup>32</sup>), a dose that is approximately 20 times above the recommended dose for adult patients for supplementation in PN. This information provides additional evidence to not exceed recommended doses of zinc supplementation in PN, especially for prolonged durations, as hypocupremia can result in reversible (anemia, leukopenia, proteinuria) and sometimes irreversible (myeloneuropathy) complications.

(b) (4)

The medical literature search also identified four cases of hypersensitivity reactions with insulin-containing zinc preparations. The four cases of hypersensitivity occurred after treatment with zinc-containing insulin and all reported a lack of symptoms after administration of zinc-free insulin (or a reduced amount of zinc). Additionally, three of four cases reported additional testing to confirm a zinc allergy. These cases suggest that it may be possible to have an allergy to zinc, although this is a naturally occurring mineral that we consume in our diet.<sup>2</sup> A general contraindication statement to avoid use in patients with known hypersensitivity to any component of the formulation should be added to the product label.

Lastly, the literature search identified two cases of seizure [REDACTED] (b) (4) [REDACTED] one case was deemed possible, although other etiologies could not be ruled out and the other case was unassessable.

## 5 CONCLUSION

In conclusion, our analysis of multiple data sources 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, we identified multiple adverse events (e.g., hypocupremia, hypersensitivity, overdose-related cardiac failure) reported with various zinc preparations (e.g., oral, parenteral, hemodialysis fluids, zinc-containing insulin), especially when used at high doses.

## 6 RECOMMENDATIONS

Based on this review, DPV-I recommends the following:

- Addition of case details from the preterm infant overdose case to the OVERDOSAGE section.
- [REDACTED] (b) (4)
- Addition of a general contraindication statement to avoid use in patients with known hypersensitivity to any component of the formulation.
- Addition of hypocupremia and associated anemia, leukopenia, neutropenia, thrombocytopenia, myeloneuropathy, and nephrotic-range proteinuria to OVERDOSAGE with the following recommended verbiage:

Several postmarketing case reports have found that high doses of supplemental zinc (above the recommended doses of Injectable Zinc Sulfate) taken over extended periods of time (i.e., months to years) may result in decreased copper absorption in the intestines and copper deficiency. The cases reported the following complications of copper deficiency: anemia, leukopenia, neutropenia, thrombocytopenia, pancytopenia, myeloneuropathy, and nephrotic-range proteinuria.

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.

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

## 7.2 APPENDIX B. 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.

### 7.3 APPENDIX C. LINE LISTING OF REPORTS SUBMITTED BY APPLICANT

	Initial FDA Received Date	FAERS Case #*	Version #	Manufacturer Control #	Case Type*	Age (years)	Sex	Suspect Product(s)	Country Derived	Serious Outcome(s)†
1	10/23/2008	6803804	1	20080288†	Expedited (15-Day)	35	Female	Calcium Gluconate Injection	USA	HO
2	10/23/2008	6803803	1	20080296†	Expedited (15-Day)	62	Female	Calcium Gluconate Injection	USA	HO
3				20090350	Non-reportable (invalid)	NR	NR	MTE-5 Injection	Korea	
4				20100582	Non-reportable (invalid)	NR	NR	MTE-5 Injection	USA	
5	04/14/2011	7930336	3	20110212	Expedited (15-Day)	1 day	Female	MTE-4 Pediatric, Calcium Gluconate	USA	LT, OT
6				20120045	Periodic	47	Female	MTE-5 Injection	USA	
7	02/21/2012	8441696	2	20120068	Expedited (15-Day)	40	Male	Calcium Gluconate Injection, MTE-5 Injection	USA	OT
8	02/21/2012	8441732	2	20120070	Expedited (15-Day)	66	Female	Calcium Gluconate Injection, MTE-5 Injection	USA	HO, OT
9				20120071	Periodic	77	Female	Calcium Gluconate Injection, MTE-5 Injection	USA	
10				20120072	Periodic	68	Female	Calcium Gluconate Injection, MTE-5 Injection	USA	
11				20120074	Periodic	71	Male	Calcium Gluconate Injection, MTE-5 Injection	USA	
12				20120442	Periodic	Neonate	NR	MTE-5 Injection, Concentrated MTE-5 Injection	USA	
13	12/18/2012	8986052	1	20120748	Expedited (15-Day)	80	Male	MTE-4 Concentrate	USA	OT
14	03/23/2015	10953016	1	20150149	Expedited (15-Day)	NR	Female	MTE-5 Injection	NR	LT, DS
15	10/12/2015	11621332	3	20150776	Expedited (15-Day)	30	Female	Concentrated Zinc Sulfate injection	USA	OT
16	10/12/2015	11621333	3	20150777	Expedited (15-Day)	NR	Male	Concentrated Zinc Sulfate injection	USA	OT
17				20170896	Periodic	NR	NR	MTE-5 Injection	USA	
18				20171310	Periodic	NR	Female	MTE-5 Injection	USA	

\* No corresponding FAERS case # found for periodic or invalid reports. Reports assessed as invalid if there was no identifiable patient.

†Zinc Sulfate listed as a concomitant medication only.

‡ 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, LT= Life-threatening, DS= Disability, OT=Other medically significant, NR=Not reported

## 7.5 APPENDIX D. LINE LISTING OF REPORTS RETRIEVED BY FAERS DATABASE\*

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s) <sup>†</sup>
1	4/15/2019	16198491	1	US-AMREGENT-20190691	Expedited (15-Day)	.5	FEMALE	USA	DE
2	6/19/2014	10252595	1	2014AP003362	Expedited (15-Day)	15	FEMALE	USA	OT
3	8/16/2013	9461825	1	TR-US-EMD SERONO, INC.-7228592	Expedited (15-Day)		FEMALE	TUR	HO
4	7/20/1984	4405085	1		Non- Expedited	43	FEMALE	USA	OT
5	3/31/2016	12227031	1	FR-BAUSCH-BL-2016-007014	Expedited (15-Day)	24	FEMALE	FRA	HO,OT
6	2/14/2014	9908095	1		Direct		NULL	USA	OT
7	9/9/2013	9508074	1	PHHY2013GB095916	Expedited (15-Day)	75	FEMALE	GBR	HO,OT
8	9/30/2018	15449159	2	GB-BAXTER-2018BAX024341	Expedited (15-Day)	69	MALE	GBR	HO
9	1/8/2019	15798057	2	GB-PFIZER INC-2019006590	Expedited (15-Day)	69	MALE	GBR	HO
10	8/20/2013	9474966	1	7228592	Expedited (15-Day)	5	FEMALE	TUR	HO
11	9/9/2013	9515665	1	GER/UKI/13/0034413	Expedited (15-Day)	75	FEMALE	GBR	HO,OT
12	9/11/2013	9521603	1	AUR-APL-2013-07446	Expedited (15-Day)	75	FEMALE	GBR	HO,OT
13	9/13/2013	9523623	1	GB-BAYER-2013-106516	Expedited (15-Day)	75	FEMALE	GBR	HO,OT
14	9/16/2013	9524257	1	GB-RANBAXY-2013R1-72993	Expedited (15-Day)	75	FEMALE	GBR	HO,OT
15	9/16/2013	9525148	1	GB-MYLANLABS-2013S1019843	Expedited (15-Day)	75	FEMALE	GBR	HO,OT
16	9/16/2016	12756057	1	AR-FRESENIUS KABI-FK201606591	Expedited (15-Day)	.3275	MALE	ARG	OT
17	9/16/2016	12756043	1	AR-FRESENIUS KABI-FK201606592	Expedited (15-Day)	.02738	MALE	ARG	OT
18	7/29/2014	10349065	1	GB-BAXTER-2014BAX041022	Expedited (15-Day)	55	FEMALE	GBR	HO
19	2/7/1986	4473386	1	M323	Expedited (15-Day)		MALE	USA	DE
20	10/10/2014	10511675	4	PHHY2014US118991	Expedited (15-Day)		FEMALE	USA	HO,OT
21	3/1/2004	4101036	1		Direct	60	MALE	USA	
22	4/12/2016	12257125	1	FR-TEVA-651173ISR	Expedited (15-Day)	24	FEMALE	FRA	HO
23	4/18/2016	12278052	1	FR-SUN PHARMACEUTICAL INDUSTRIES LTD-2016RR-114968	Expedited (15-Day)	24	FEMALE	FRA	HO,OT
24	6/14/2016	12462574	1	FR-LUPIN PHARMACEUTICALS INC.-2016-01373	Non- Expedited	24	FEMALE	FRA	HO
25	10/18/2016	12856171	1	SE-CIPLA LTD.-2016BD19581	Expedited (15-Day)		NULL	BGD	OT
26	10/18/2016	12856173	1	SE-CIPLA LTD.-2016BD19582	Expedited (15-Day)		NULL	BGD	OT
27	10/18/2016	12856189	1	SE-CIPLA LTD.-2016BD19586	Expedited (15-Day)		NULL	BGD	OT
28	10/18/2016	12856239	1	SE-CIPLA LTD.-2016BD19595	Expedited (15-Day)		NULL	BGD	OT
29	10/18/2016	12856306	1	SE-CIPLA LTD.-2016BD19594	Expedited (15-Day)		NULL	BGD	OT
30	10/19/2016	12860528	1	SE-CIPLA LTD.-2016BD19681	Expedited (15-Day)		NULL	BGD	DE,OT
31	10/19/2016	12860565	1	SE-CIPLA LTD.-2016BD19701	Expedited (15-Day)		NULL	BGD	DE,OT
32	10/19/2016	12860586	1	SE-CIPLA LTD.-2016BD19700	Expedited (15-Day)		NULL	BGD	DE,OT
33	10/19/2016	12860642	1	SE-CIPLA LTD.-2016BD19702	Expedited (15-Day)		NULL	BGD	DE,OT
34	10/19/2016	12860823	1	SE-CIPLA LTD.-2016BD19698	Expedited (15-Day)		NULL	BGD	OT
35	10/19/2016	12860826	1	SE-CIPLA LTD.-2016BD19697	Expedited (15-Day)		NULL	BGD	OT
36	10/19/2016	12860841	1	SE-CIPLA LTD.-2016BD19699	Expedited (15-Day)		NULL	BGD	OT
37	10/19/2016	12860844	1	SE-CIPLA LTD.-2016BD19709	Expedited (15-Day)		NULL	BGD	OT
38	10/19/2016	12860849	1	SE-CIPLA LTD.-2016BD19710	Expedited (15-Day)		NULL	BGD	OT
39	10/19/2016	12860939	1	SE-CIPLA LTD.-2016BD19711	Expedited (15-Day)		NULL	BGD	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)†
40	10/19/2016	12860941	1	SE-CIPLA LTD.-2016BD19741	Expedited (15-Day)		NULL	BGD	OT
41	10/19/2016	12860947	1	SE-CIPLA LTD.-2016BD19742	Expedited (15-Day)		NULL	BGD	OT
42	10/19/2016	12860949	1	SE-CIPLA LTD.-2016BD19740	Expedited (15-Day)		NULL	BGD	OT
43	10/19/2016	12860978	1	SE-CIPLA LTD.-2016BD19739	Expedited (15-Day)		NULL	BGD	OT
44	10/19/2016	12860984	1	SE-CIPLA LTD.-2016BD19738	Expedited (15-Day)		NULL	BGD	OT
45	10/19/2016	12861016	1	SE-CIPLA LTD.-2016BD19744	Expedited (15-Day)		NULL	BGD	OT
46	10/19/2016	12861026	1	SE-CIPLA LTD.-2016BD19743	Expedited (15-Day)		NULL	BGD	OT
47	10/19/2016	12861343	1	SE-CIPLA LTD.-2016BD19746	Expedited (15-Day)		NULL	BGD	OT
48	10/19/2016	12861368	1	SE-CIPLA LTD.-2016BD19745	Expedited (15-Day)		NULL	BGD	OT
49	10/19/2016	12861547	1	SE-CIPLA LTD.-2016BD19708	Expedited (15-Day)		NULL	BGD	OT
50	10/19/2016	12861565	1	SE-CIPLA LTD.-2016BD19707	Expedited (15-Day)		NULL	BGD	OT
51	10/19/2016	12861788	1	SE-CIPLA LTD.-2016BD19706	Expedited (15-Day)		NULL	BGD	OT
52	12/27/2017	14329190	1	IT-FRESENIUS KABI-FK201711030	Expedited (15-Day)	4	MALE	ITA	HO
53	7/13/2018	15138400	1	US-STRIDES ARCOLAB LIMITED-2018SP005842	Expedited (15-Day)		NULL	USA	OT
54	10/29/2018	15563793	1	IE-BAXTER-2018BAX026202	Expedited (15-Day)		FEMALE	IRL	HO
55	4/13/2018	14759387	1	IE-SA-2018SA106070	Expedited (15-Day)	70	FEMALE	IRL	HO
56	10/16/2018	15506896	1	GB-PFIZER INC-2018408008	Expedited (15-Day)	53	MALE	GBR	OT
57	6/11/2004	4153230	1	JP-MERCK-0401USA01644	Expedited (15-Day)	27	MALE	JPN	OT
58	3/20/2015	10933085	1	PR-BAXTER-2015BAX012121	Non- Expedited	.91667	FEMALE	PRI	
59	4/22/2015	11056227	2	PR-BAXTER-2015BAX021450	Non- Expedited		NULL	PRI	
60	6/1/2015	11153196	1	US-BAXTER-2015BAX026756	Non- Expedited		NULL	USA	
61	2/18/2016	12093256	1		Direct		NULL	USA	
62	8/2/1993	5796051	1		Direct		NULL	USA	
63	1/31/1996	5695482	1		Direct		NULL	USA	
64	2/7/1996	5792943	1		Direct		NULL	USA	
65	8/7/1996	5786660	1		Direct		NULL	USA	
66	5/24/1991	4799924	1		Direct		FEMALE	USA	
67	3/15/1991	4783655	1		Direct	59	FEMALE	USA	DE,HO,OT
68	9/22/2014	10467076	1	PHHY2014PK118648	Expedited (15-Day)	33	FEMALE	PAK	OT
69	12/1/1977	4321309	1		Direct	55	MALE	USA	
70	4/22/2014	10094340	4	US-BRISTOL-MYERS SQUIBB COMPANY-19964170	Non- Expedited	33.344	FEMALE	USA	
71	10/12/2015	11621332	3	US-LPDUSPRD-20150776	Expedited (15-Day)	30	FEMALE	USA	OT
72	10/12/2015	11621333	3	US-LPDUSPRD-20150777	Expedited (15-Day)		MALE	USA	OT
73	7/1/1976	4307632	1		Direct	36	FEMALE	USA	OT
74	2/17/2004	4093712	1		Direct	55	FEMALE	USA	OT
75	3/4/2004	4104777	1		Direct	39	FEMALE	USA	HO
76	9/12/2008	6755385	1	CA-JNCH-2008023133	Expedited (15-Day)		FEMALE	CAN	OT
77	9/27/2004	4222260	1	2004066276	Expedited (15-Day)	76.27	FEMALE	USA	OT
78	7/16/2008	6711471	1	2008018000	Expedited (15-Day)	82	MALE	USA	OT
79	4/22/2008	6634950	1	2008009356	Expedited (15-Day)	53	FEMALE	USA	OT
80	6/9/2005	5822337	1	2005080788	Expedited (15-Day)	32	FEMALE	USA	OT
81	1/25/2008	6545387	1	2008001358	Expedited (15-Day)		NULL	USA	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s) <sup>†</sup>
82	5/21/2008	6657339	2	2008012223	Expedited (15-Day)		MALE	USA	OT
83	2/9/2004	4088399	1		Direct	69	FEMALE	USA	OT
84	2/9/2004	4088449	1		Direct	51.25	FEMALE	USA	DS,OT
85	2/12/2004	4091569	1		Direct	57.18	FEMALE	USA	OT
86	2/12/2004	4091540	1		Direct	43.67	FEMALE	USA	OT
87	2/17/2004	4093714	1		Direct	60	MALE	USA	OT
88	2/17/2004	4093715	1		Direct	46	FEMALE	USA	OT
89	3/1/2004	4101698	1		Direct	49	MALE	USA	OT
90	6/29/2011	8037236	1	2011-00753	Expedited (15-Day)		FEMALE	USA	
91	6/29/2011	8037251	1	2011-00752	Expedited (15-Day)		MALE	USA	
92	7/5/2011	8040991	1	2011-00845	Expedited (15-Day)		FEMALE	USA	
93	7/12/2011	8053927	1	2011-00902	Expedited (15-Day)		FEMALE	USA	
94	7/12/2011	8053933	1	2011-00901	Expedited (15-Day)		MALE	USA	
95	7/12/2011	8053935	1	2011-00920	Expedited (15-Day)		MALE	USA	
96	7/29/2011	8082102	1	2011-01203	Expedited (15-Day)		MALE	USA	
97	12/19/2011	8314898	1	2011-01329	Expedited (15-Day)		FEMALE	USA	OT
98	2/10/2004	4089350	1		Direct	52	MALE	USA	DS
99	8/25/1986	4502765	1		Direct		UNKNOW N	USA	OT
100	2/2/1994	5093595	1		Direct	24	MALE	USA	DS,HO,LT,R I,OT
101	11/21/2000	3570210	1	2834	Expedited (15-Day)	89	MALE	USA	DE,OT
102	11/21/2000	3572129	1	2830	Expedited (15-Day)	88	FEMALE	USA	DE,OT
103	11/21/2000	3572136	1	2835	Expedited (15-Day)	87	MALE	USA	HO,OT
104	1/28/2004	4073717	1	WAES 0401USA01644	Expedited (15-Day)	27	MALE	JPN	OT
105	7/5/2006	6084720	1		Direct	58	FEMALE	USA	DS
106	3/15/2012	8461482	1	GB-BAXTER-2012BH007318	Expedited (15-Day)	.58333	FEMALE	GBR	DE
107	7/17/2014	10330717	1	FK201402767	Expedited (15-Day)	55	FEMALE	GBR	HO
108	8/12/2016	12648343	1	BR-FRESENIUS KABI-FK201605378	Expedited (15-Day)	.05476	FEMALE	BRA	LT
109	10/17/2016	12852914	1	SE-CIPLA LTD.-2016BD19587	Expedited (15-Day)		NULL	BGD	DE,OT
110	10/11/2018	15487215	1	GB-BAXTER-2018BAX025138	Expedited (15-Day)	53	MALE	GBR	OT
111	7/16/2010	7492243	1		Direct	33.43	FEMALE	USA	
112	1/17/2012	8338602	1	US-PFIZER INC-2012009373	Non- Expedited		FEMALE	USA	
113	10/6/2014	10504085	2	ADR-2014-01656	Expedited (15-Day)		FEMALE	USA	HO,OT
114	7/29/2014	10349062	1	IT-BAXTER-2014BAX041035	Expedited (15-Day)		FEMALE	ITA	OT
115	3/2/2016	12138641	1	RU-TEVA-637554ISR	Expedited (15-Day)	39	NULL	RUS	HO
116	9/16/2016	12756058	1	AR-FRESENIUS KABI-FK201606587	Expedited (15-Day)	60.62	FEMALE	ARG	OT
117	1/3/2012	8319910	1	TR-ROCHE-1024281	Expedited (15-Day)	6	MALE	TUR	OT
118	12/26/2013	9783870	4	US-PFIZER INC-2013365225	Non- Expedited	83	FEMALE	USA	
119	3/28/2018	14690942	1	PHEH2018US011825	Non- Expedited		FEMALE	USA	
120	2/4/2019	15909210	1	US-ABBVIE-18K-163-2258688-00	Non- Expedited		FEMALE	USA	
121	2/5/1986	4475772	1	M323	Expedited (15-Day)	1 month	MALE	USA	DE
122	3/16/2012	8462734	1	GB-BAXTER-2012BH007173	Expedited (15-Day)		NULL	GBR	LT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s) <sup>†</sup>
123	7/11/2008	6697231	1	US-BAXTER-2008BH006172	Expedited (15-Day)	.91667	FEMALE	USA	HO,OT
124	12/17/2012	8967934	1	IT-BAXTER-2012BAX026758	Expedited (15-Day)		MALE	ITA	HO
125	4/4/2018	14715445	1	IE-BAXTER-2018BAX009645	Expedited (15-Day)	70.710 47	FEMALE	IRL	HO
126	12/2/2015	11795370	1	IE-BAXTER-2015BAX062965	Expedited (15-Day)	55	FEMALE	IRL	HO
127	11/20/1985	4467209	1	M317	Expedited (15-Day)	10	FEMALE	USA	DE
128	6/14/1999	3287251	1	10017010	Expedited (15-Day)	32.58	FEMALE	DEU	HO
129	9/14/2018	15386804	2	GB-FRESENIUS KABI-FK201809581	Expedited (15-Day)	69.412 73	MALE	GBR	HO
130	12/13/2017	14281182	1	IT-BAXTER-2017BAX040893	Expedited (15-Day)	4	MALE	ITA	HO
131	6/11/2018	14995876	2	US-VIVIMED-2018SP004373	Expedited (15-Day)		NULL	USA	OT
132	12/29/2003	4055666	1		Direct	86	FEMALE	USA	OT

\* Excludes duplicate reports (n=30) and topical Zinc (n=1).

† 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: DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, CA= Congenital Anomaly, OT=Other medically significant, NR=not reported

## 7.6 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)*
1	11/30/04	74096	MANDATORY	NR	NR	ONDRA PHARMACEUTICAL ZINC SULFATE	USA	OT
2	08/23/07	95710	VOLUNTARY	NR	M	SPRING VALLEY NATURAL ZINC, 50 MG.	NR	
3	11/06/07	97806	MANDATORY	NR	F	SPRING VALLEY ZINC CAPSULES 50 MG	NR	
4	03/05/08	100999	VOLUNTARY	NR	NR	PHARMASSURE ZINC GLUCONATE	NR	
5	09/01/09	117397	MANDATORY	NR	NR	VITAENERGY URINOZINC SUPPLEMENT	USA	
6	07/23/10	128352	MANDATORY	33	F	JLM PHARMATECH ZINCATE CAPSULE	USA	
7	10/27/10	131418	VOLUNTARY	12	M	KIRKMAN LABS LIQUID ZINC	USA	
8	03/29/11	137269	MANDATORY	39	F	ZINC 50MG 2E3 (ZINC) TABLET	USA	OT
9	05/11/11	138861	MANDATORY	70	F	VSB (VITAMINSHOPPE) BASIC ZINC 30 MG	USA	
10	07/06/11	140967	MANDATORY	26	F	GNC ZINC 100	USA	OT
11	10/05/11	144168	VOLUNTARY	NR	NR	SPRING VALLEY ZINC	USA	
12	12/01/11	146222	VOLUNTARY	19	F	GNC ZINC 100	USA	OT
13	04/12/12	151090	MANDATORY	36	F	ZINC 50 MG 2E3 TABLET	USA	OT
14	09/25/12	156946	MANDATORY	9	M	ZINC DRINK	USA	
15	11/07/12	158709	MANDATORY	45	F	GNC ZINC 100	USA	OT
16	03/27/13	163795	MANDATORY	47	F	SUNDOWN NATURALS ZINC 50 MG CAPLETS	USA	OT
17	11/26/13	172201	VOLUNTARY	64	M	ZINC 50 MG 2E3 (ZINC) TABLET	USA	HO
18	02/20/14	174119	VOLUNTARY	NR	NR	SPRING VALLEY ZINC	USA	HO
19	03/14/14	174591	VOLUNTARY	68	F	NATURE'S BOUNTY CHELATED ZINC 50MG CAPLETS	USA	LT
20	07/31/14	178254	VOLUNTARY	72	F	FINEST NUTRITION HIGH POTENCY ZINC 50MG TABLETS	USA	LT, OT
21	04/10/15	184672	VOLUNTARY	70	M	NATURE'S BOUNTY CHELATED ZINC 50MG CAPLETS	USA	LT
22	05/01/15	185574	VOLUNTARY	83	M	NATURALIST ZINC 50MG CAPLETS (DIETARY SUPPLEMENT) CAPLET	USA	OT
23	04/12/16	195349	MANDATORY	NR	NR	NATURE'S BOUNTY ZINC	NR	NR
24	10/17/16	202944	MANDATORY	58	M	CVS ZINC	USA	OT
25	11/03/16	203648	VOLUNTARY	86	M	PURITAN'S PRIDE CHELATED ZINC 25MG TABLETS	USA	HO, OT
26	09/14/17	2017-CFS-000089	VOLUNTARY	22	M	ZINC GLUCONATE	USA	
27	09/27/17	2017-CFS-000349	MANDATORY	63	M	BIO ZINC	USA	OT
28	11/14/17	2017-CFS-001750	VOLUNTARY	41	F	GNC ZINC	Canada	LT
29	12/27/17	2017-CFS-002999	MANDATORY	75	F		USA	OT
30	06/21/18	2018-CFS-008406	MANDATORY	68	F		USA	
31	10/19/18	2018-CFS-012700	VOLUNTARY	74	F	NATURE'S BLEND 100 MG	USA	LT

\* Excludes duplicate reports (n=2) and Zinc as a component of MVI products (n=400), topical cosmetics (n=6), or infant formula (n=4)

† 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: DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, CA= Congenital Anomaly, OT=Other medically significant, NR=not reported

## 7.7 APPENDIX F. LINE LISTING OF CASES RETRIEVED IN MEDICAL LITERATURE

	CITATION	AGE	GENDER	ROUTE	DOSING	DURATION	HYPOCUPREMIA	ANEMIA	LEUKOPENIA	THROMBOCYTOPENIA	NEUROPATHY	NEPHROPATHY	SEIZURES	HYPERSENSITIVITY
1	Porter K.G., et al. (1977) "Anaemia and low serum-copper during zinc therapy." 2(8041):774.	59	F	PO	Zinc sulfate 220 mg 3x daily for 14 months	14 months	X	X	X†		§			
2	Prasad, A. S., et al. (1978). "Hypocupremia induced by zinc therapy in adults." JAMA 240(20): 2166-2168.	26	M	PO	Zinc sulfate 220 mg three times daily for 9 months, then zinc sulfate 110 mg 6x daily for 14 months, then zinc acetate (25 mg of elemental zinc) 6-8x daily for 40 days	24 months	X	X	X†					
3	Patterson, W. P., et al. (1985). "Zinc-induced copper deficiency: megamineral sideroblastic anemia." Ann Intern Med 103(3): 385-386.	57	M	PO	450 mg daily for 2 years	2 years	X	X	X†					
4	Hoffman, H. N., 2nd, et al. (1988). "Zinc-induced copper deficiency." Gastroenterology 94(2): 508-512.	35	F	PO	Zinc sulfate 440-660 mg daily for 10 months + zinc-containing vitamin daily (zinc sulfate 80mg)	10 months	X	X	X†					
5	Simon, S. R., et al. (1988). "Copper deficiency and sideroblastic anemia associated with zinc ingestion." Am J Hematol 28(3): 181-183.	44	M	PO	Zinc gluconate 200-300 mg daily for 2+ years	2+ years	X	X	X†					
6a	Broun, E. R., et al. (1990). "Excessive zinc ingestion. A reversible cause of sideroblastic anemia and bone marrow depression." JAMA 264(11): 1441-1443.	31	M	CI	N/A		X	X	X					
6b		48	M	PO	Daily for 2 years	2 years		X	X					
7	Gyorffy, E. J. and H. Chan (1992). "Copper deficiency and microcytic anemia resulting from prolonged ingestion of over-the-counter zinc." Am J Gastroenterol 87(8): 1054-1055.	58	M	PO	Zinc-amino acid chelate 1008 mg (810 mg elemental zinc) daily for 18 months	18 months	X	X						
8	Fiske, D. N., et al. (1994). "Zinc-induced sideroblastic anemia: report of a case, review of the literature, and description of the hematologic syndrome." Am J Hematol 46(2): 147-150.	25	M	PO	300-600 mg daily for 18 months, then 1600 mg daily for 1 month	19 months	X	X	X†			X		
9	Bennett, D. R., et al. (1997). "Zinc toxicity following massive coin ingestion." Am J Forensic Med Pathol 18(2): 148-153.	55	M	CI	N/A		X	X						

	<b>CITATION</b>	<b>AGE</b>	<b>GENDER</b>	<b>ROUTE</b>	<b>DOSING</b>	<b>DURATION</b>	<b>HYPOCUPREMIA</b>	<b>ANEMIA</b>	<b>LEUKOPENIA</b>	<b>THROMBOCYTOPENIA</b>	<b>NEUROPATHY</b>	<b>NEPHROPATHY</b>	<b>SEIZURES</b>	<b>HYPERSENSITIVITY</b>
10	Prodan C.I. and N.R. Holland. (2000) "CNS demyelination from zinc toxicity?" Neurology. 54:1704-6.	45	M	UNK			X	X	X		X			
11	Prodan C.I., et al. (2002) "CNS demyelination associated with copper deficiency and hyperzincemia." Neurology. 59:1453-1456.	45	F	UNK			X	X	X†		X			
12	Kumar, N., et al. (2003). "Myelopathy due to copper deficiency." Neurology 61(2): 273-274.	65	M	PO	200-400 mg daily for 22 years	22 years	X				X			
13	Hein, M. S. (2003). "Copper deficiency anemia and nephrosis in zinc-toxicity: a case report." S D J Med 56(4): 143-147.	22	F	PO	Zinc gluconate 2000-2300 mg daily for 12 months	12 months	X	X	X†			X		
14	Hedera, P., et al. (2003). "Myelopolyneuropathy and pancytopenia due to copper deficiency and high zinc levels of unknown origin: further support for existence of a new zinc overload syndrome." Arch Neurol 60(9): 1303-1306.	46	M	UNK			X	X			X			
15	Greenberg, S. A. and H. R. Briemberg (2004). "A neurological and hematological syndrome associated with zinc excess and copper deficiency." J Neurol 251(1): 111-114.	43	F	UNK			X	X	X†		X			
16	Bartner, R., et al. (2005). "Pancytopenia, arthralgia and myeloneuropathy due to copper deficiency." Medizinische Klinik 100(8): 497-501. (German)	71	F	UNK			X	X	X†	‡	X	X		
17a	Willis, M. S., et al. (2005). "Zinc-induced copper deficiency: a report of three cases initially recognized on bone marrow examination." Am J Clin Pathol 123(1): 125-131.	21	M	PO	600 mg daily	5 years	X	X	X†					
17b		42	M	DP	1 tube daily for 4-5 years	4-5 years	X	X	X†		X			
17c		47	M	UNK			X	X	X†		X			
18	Rowin, J. and S. L. Lewis (2005). "Copper deficiency myeloneuropathy and pancytopenia secondary to overuse of zinc supplementation." J Neurol Neurosurg Psychiatry 76(5): 750-751.	53	F	PO	Zinc gluconate 200-400 mg daily for 1+ years	1+ years	X	X	X		X			

	<b>CITATION</b>	<b>AGE</b>	<b>GENDER</b>	<b>ROUTE</b>	<b>DOSING</b>	<b>DURATION</b>	<b>HYPOCUPREMIA</b>	<b>ANEMIA</b>	<b>LEUKOPENIA</b>	<b>THROMBOCYTOPENIA</b>	<b>NEUROPATHY</b>	<b>NEPHROPATHY</b>	<b>SEIZURES</b>	<b>HYPERSENSITIVITY</b>
19	Narayan SK and Kaveer N. (2006) "CNS demyelination due to hypocupremia in Wilson's disease from overzealous treatment." <i>Neurology India</i> . 54(1):110-111.	13	M	PO	Zinc sulfate 280 mg daily for 4 years	4 years	X	X			X			
20	Yaldizli, Ö., et al. (2006). "Copper deficiency myelopathy induced by repetitive parenteral zinc supplementation during chronic hemodialysis." <i>J Neurol</i> 253(11): 1507-1509.	61	F	HD	140 mg during each dialysis for 6 years	6 years	X	X			X			
21a	Nations, S. P., et al. (2008). "Denture paste. An unusual source of excess zinc, leading to hypocupremia and neurologic disease." <i>Neurology</i> 71(9): 639-643.	41	F	DP	2 tubes weekly for 3.5 years	3 5 years	X		X		X			
21b		42	F	DP	3 tubes per week for many years	many years	X				X			
22	Videt-Gibou, D., et al. (2010). "Acquired copper deficiency myelopathy." <i>Revue Neurologique</i> 166(6-7): 639-643. (French)	57	M	DP			X	X	X <sup>†</sup>		X	X		
23	Horvath, J., et al. (2010). "Zinc-induced copper deficiency in Wilson disease." <i>Journal of Neurology, Neurosurgery and Psychiatry</i> 81(12): 1410-1411.	25	M	PO	Zinc sulfate 880 mg daily for 14 years, then 1100 mg daily for 1 year	15 years	X	X	X		X	X		
24	da Silva-Junior, F. P., et al. (2011). "Copper deficiency myeloneuropathy in a patient with Wilson disease." <i>Neurology</i> 76(19): 1673-1674.	44	F	PO	Zinc acetate 150 mg three times daily for 14 years	14 years	X		X	X	X			
25	Teodoro, T., et al. (2013). "Recovery after copper-deficiency myeloneuropathy in Wilson's disease." <i>J Neurol</i> 260(7): 1917-1918.	36	M	PO	Zinc sulfate 150 mg daily for 16 years, then zinc sulfate 330 mg daily for 3 years, then zinc acetate 100 mg daily for 11 months	20 years	X	X			X			
26	Sakamaki, Y., et al. (2014). "Nephrotic syndrome and end-stage kidney disease accompanied by bicytopenia due to copper deficiency." <i>Internal Medicine</i> 53(18): 2101-2106.	73	M	PO	Polaprezinc (zinc and L-carnosine) for several months	several months	X	X	X <sup>†</sup>			X		
27	Rissardo, J. P. and A. L. F. Caprara (2019). "Copper deficiency myelopathy secondary to parenteral zinc supplementation during chronic dialysis." <i>Neurology Asia</i> 24(1): 79-82.	65	F	HD	100-150 mg 3-5 times weekly for 10 years	10 years	X	X			X			

	<b>CITATION</b>	<b>AGE</b>	<b>GENDER</b>	<b>ROUTE</b>	<b>DOSING</b>	<b>DURATION</b>	<b>HYPOCUPREMIA</b>	<b>ANEMIA</b>	<b>LEUKOPENIA</b>	<b>THROMBOCYTOPENIA</b>	<b>NEUROPATHY</b>	<b>NEPHROPATHY</b>	<b>SEIZURES</b>	<b>HYPERSENSITIVITY</b>
28	Tasic V, et al. (1982). "Zinc toxicity." Pediatrics. 70(4): 660-661.	Premature infant		UNK	Zinc sulfate 3 mg/kg								X	
29	Green AL and Weaver DF. (2008) "Potential proconvulsant effects of oral zinc supplementation – A case report." NeuroToxicology. 29(3):476-477.	28	M	PO									X	
30a	Feinglos MN and Jegasothy BV. (1979 Jan 20) "Insulin" allergy due to zinc. The Lancet. 1(8108):122-124.	64	M	SubQ										X
30b		48	F	SubQ										X
31	Bruni B, Campana M, Gamba S, Grassi G, Blatto A. (1985 Mar-Apr) "A generalized allergic reaction due to zinc in insulin preparation." Diabetes Care. 8(2):201.	61	M	SubQ										X
32	Ammar IB, et al. (2012) "Generalized allergy due to zinc in insulin treated with zinc-free insulin." Acta Diabetol 49:239-41.	61	M	SubQ										X

\* Elemental zinc concentrations: 23% of zinc sulfate, 14.3% of zinc gluconate, 30% of zinc acetate, 80% of zinc oxide.  
† Case also noted neutropenia.  
‡ Case noted pancytopenia, although it did not specify thrombocytopenia.  
§ Case noted peripheral neuropathy, but no temporal relationship to zinc intake was described.  
Legend: PO=oral; DP=denture paste; HD=hemodialysis fluid; CI=coin ingestion; SubQ=subcutaneous; UNK=unknown; OTC=over-the counter; N/A=not applicable

## 8 REFERENCES

- <sup>1</sup> Jeejeebhoy K. Zinc: an essential trace element for parenteral nutrition. *Gastroenterology*. 2009; 137(5)(suppl):S7-S12.
- <sup>2</sup> Otten JJ, Pitz Hellwig J, Meyers LD, eds. *Dietary Reference Intakes: The Essential Guide to Nutrition Requirements*. Washington DC: National Academies Press; 2006.
- <sup>3</sup> McGrath J. Acrodermatitis Enteropathica. National Organization for Rare Disorders. 2015. Available at: <https://rarediseases.org/rare-diseases/acrodermatitis-enteropathica/>.
- <sup>4</sup> U.S. Department of Health and Human Services. National Institutes of Health, Office of Dietary Supplements. (Updated March 13, 2019). Zinc. Retrieved from: <https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/>.
- <sup>5</sup> Hooper, P. L., et al. (1980). "Zinc lowers high-density lipoprotein-cholesterol levels." *JAMA* 244(17): 1960-1961.
- <sup>6</sup> Wazir SM and Ghobrial I. Copper deficiency, a new triad: anemia, leucopenia, and myeloneuropathy. *J Community Hosp Intern Med Perspect*. Oct 2017; 7(4):265-268.
- <sup>7</sup> Roberts EA and Schilsky ML.; American Association for Study of Liver Diseases (AASLD). Diagnosis and Treatment of Wilson Disease: An Update. *Hepatology*. June 2008; 47(6):2089-2111.
- <sup>8</sup> Vanek VW, et al. (2012) A.S.P.E.N. Position Paper: Recommendations for Changes in Commercially Available Parenteral Multivitamin and Multi-Trace Element Products. Nutrition in clinical practice: official publication of the American Society for Parenteral and Enteral Nutrition. 27. 440-91. Available at: <https://www.researchgate.net/publication/228063959 ASPEN Position Paper Recommendations for Changes in Commercially Available Parenteral Multivitamin and Multi-Trace Element Products>.
- <sup>9</sup> Mirtallo J, Canada T, Johnson D, et al; Task Force for the Revision of Safe Practices for Parenteral Nutrition. Safe practices for parenteral nutrition [published correction appears in *JPEN J Parenter Enteral Nutr*. 2006;30:177] *JPEN J Parenter Enteral Nutr*. 2004;28(6):S39-S70.
- <sup>10</sup> Greene HL, Hambridge M, Schanler R, Tsang R. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infant 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;48:1324-1342.
- <sup>11</sup> Tsang R, Uauy R, Koletzko B, Zlotkin SH, eds. *Nutrition of the Preterm Infant: Scientific Basis and Practical Guidelines*. Cincinnati, OH: Digital Educational Publishing. 2005.
- <sup>12</sup> Zinc sulfate [package insert]. American Regent, Inc. Shirley NY. Label updated December 19, 2018. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1a03fe85-fdc9-4847-960f-1fc782d7d493>.
- <sup>13</sup> Zinc Sulfate Injection [package insert]. American Regent, Inc. Shirley NY. Proposed package insert submitted October 24, 2018. Available at: [Application 209377 - Sequence 0004 - zinc-sulfate-pi-final](#).
- <sup>14</sup> American Regent, Inc. [Response to information request: Clinical](#). February 14, 2019. Available at: [Application 209377 - Sequence 0010 - cover letter-response to information-14feb2019](#).
- <sup>15</sup> American Regent, Inc. [Response to information request: Clinical](#). May 31, 2019. Available at: [Application 209377 - Sequence 0022 - efficacy-info-amend-response-to-ir-31may2019](#).
- <sup>16</sup> The use of the WHO\_UMC system for standardized case causality assessment. Retrieved 12/4/18 from [http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/WHOcausality\\_assessment.pdf](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf).
- <sup>17</sup> Grissinger M. A Fatal Zinc Overdose in a Neonate; Confusion of Micrograms with Milligrams. *Pharmacy and Therapeutics* 2011; 36(7): 393-94/409.
- <sup>18</sup> Hudspeth M, Turner A, Miller N, and Lazarchick J. Pancytopenia after allogeneic bone marrow transplant due to copper deficiency. *J Pediatr Hematol Oncol*. May 2014; 36(4):316-318.
- <sup>19</sup> Willis, M. S., et al. Zinc-induced copper deficiency: a report of three cases initially recognized on bone marrow examination. *Am J Clin Pathol*. 2005; 123(1):125-131.
- <sup>20</sup> Ling VY, Wall M, Davis A, Gorniak M, and Grigoriadis G. Zinc-induced copper deficiency: a diagnostic pitfall of myelodysplastic syndrome. *Pathology*. Apr 2014; 46(3):246-248.
- <sup>21</sup> Hoffman HN, Phylly RL, and Fleming CR. Zinc-induced copper deficiency. *Gastroenterology*. Feb 1988; 94(2):508-512.
- <sup>22</sup> Gilbert A, Doussot A, Lagoutte N, Facy O, Cheynel N, and Rat P. Combined zinc sulphate and NSAID-induced gastric ulcer perforation in Wilson disease: A case report. *Clinics and Research in Hepatology and Gastroenterology*. Feb 2016; 40(1):e11-e12.
- <sup>23</sup> Galzin - zinc acetate [package insert]. Teva Select Brands. North Wales, PA. Label updated July 3, 2018. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a0c72bff-20f3-4241-b966-34a95178d1a3>.
- <sup>24</sup> A. Wiernicka, W. Jańczyk, M. Dądalski, Y. Avsar, H. Schmidt, P. Socha. Gastrointestinal side effects in children with Wilson's disease treated with zinc sulphate. *World J Gastroenterol*, 19 (27) (2013), pp. 4356-4362
- <sup>25</sup> Ciprofloxacin [package insert]. Bayer HealthCare Pharmaceuticals Inc. Whippany, NJ. Updated May 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/019537s089.020780s046lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019537s089.020780s046lbl.pdf).
- <sup>26</sup> U.S. Food and Drug Administration. Dear Manufacturer of Dietary Supplements letter, December 15, 2010. Available at: <https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/MedicationHealthFraud/UCM236985.pdf>.

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- <sup>27</sup> Porter K.G., et al. Anaemia and low serum-copper during zinc therapy. 1977; 2(8041):774.
- <sup>28</sup> European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Wilson's disease. Journal of Hepatology. 2012; 56(3):671-685.
- <sup>29</sup> Yaldizli, Ö., et al. Copper deficiency myelopathy induced by repetitive parenteral zinc supplementation during chronic hemodialysis. J Neurol. 2006; 253(11):1507-1509.
- <sup>30</sup> Rissardo, J. P. and A. L. F. Caprara. Copper deficiency myelopathy secondary to parenteral zinc supplementation during chronic dialysis. Neurology Asia. 2019; 24(1):79-82.
- <sup>31</sup> Davidsson L, et al. Zinc absorption in adult humans: the effect of protein sources added to liquid test meals. British Journal of Nutrition. 1996; 75(4):607-613.
- <sup>32</sup> Saper RB and Rash R. Zinc: An Essential Micronutrient. Am Fam Physician. May 1, 2009; 79(9):768-772.

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

Date: April 30, 2019

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Drug Name(s): zinc sulfate for parenteral nutrition

Subject: Evaluation of a Systematic Review of Medical Literature

Application Type/Number: NDA 209377 (eCTD 0002)

Applicant/sponsor: Luitpold Pharmaceuticals, Inc (currently American Regent)

OSE RCM #: 2018-2242, 2019-69

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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) evaluated a systematic literature review submitted by a Sponsor in support of NDA 209377.

NDA 209377 concerns zinc sulfate, presented as a source of zinc for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. Medical science recognizes zinc as a trace element essential to healthy human nutrition. The Sponsor seeks NDA approval through a 505(b)(2) literature-only pathway.

To support NDA 209377, the Sponsor commissioned a systematic literature review, conducted by the (b)(4) found 100 articles by systematic search for medical literature about (1) patients given zinc parenterally or (2) zinc status in patients on parenteral nutrition. Applying the (b)(4) search strategy to PubMed, DEPI updated the (b)(4) search with 34 recent articles. In addition, DEPI augmented the (b)(4) search by targeting articles found by reference-list search. This reference-list search identified nineteen pre-2015 articles not captured by (b)(4)

DEPI found that,

- (b)(4) conducted and the Sponsor reported a Systematic Literature Review, as stipulated by pre-NDA negotiations with DGIEP.
- No evidence in medical literature for toxicity or other serious adverse consequences from zinc, when administered intravenously for parenteral nutrition at conventional doses.
- Additional articles found in literature by DEPI support Luitpold's finding of "no signal of zinc toxicity" from zinc for parenteral nutrition.

DEPI identified several articles possibly used by clinical experts to justify conventional zinc dosing during parenteral nutrition. DEPI suggested that DGIEP might use information in these articles to support dose recommendations for parenteral zinc sulfate.

## 1. INTRODUCTION

### 1.1 Background

Responding to a request from the Division of Gastroenterology and Inborn Error Products (DGIEP), the Division of Epidemiology I (DEPI) evaluates a systematic literature review submitted by a Sponsor in support of NDA 209377.

NDA 209377 concerns zinc sulfate for intravenous injection, presented as a source of zinc for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. The Clinical Overviews submitted by the Sponsor (Luitpold Pharmaceuticals) propose parenteral

zinc doses of 3 mg/day in adults and 0.05 mg/kg/day in children  $\geq 10$  kg.<sup>a,b</sup>

Medical science recognizes zinc as a trace element essential to healthy human nutrition. The Institute of Medicine currently sets the adult dietary Recommended Daily Allowance (RDA) for zinc at 8 mg/day in women and 11 mg/day in men (APPENDIX 1, [1]).

Luitpold seeks NDA approval through a 505(b)(2) literature-only pathway. To identify relevant literature, Luitpold commissioned a systematic literature review, conducted by (b) (4). On January 7, 2019, DGIEP asked DEPI to evaluate “the submitted systematic literature review, including methodology, of the safety and efficacy of zinc in the adult and pediatric population.”<sup>c</sup>

## 1.2 Regulatory History

DEPI provides a timeline of events germane to DEPI’s review of NDA 209377.

Date	Event
(b) (4)	

October 22, 2018 Luitpold submits Clinical Overviews and Summaries of Clinical Safety. See NDA 209377, eCTD 0002.

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<sup>a</sup> This review refers to the Sponsor, currently American Regent, by a previous name, Luitpold.

<sup>b</sup> Clinical Overview – Adult, p 19. Clinical Overview – Pediatric, p 17.

<sup>c</sup> Vu, T, Request for Consultation, filed under NDA 209377 on January 7, 2019 (Reference ID: 4372439).

December 7, 2018 FDA Information Request asks Luitpold to cross-reference sections in NDA 209377 (b) (4) See NDA 209377, Reference ID 4360194.

## 2. REVIEW MATERIALS

DEPI reviews the following documents, submitted to NDA 209377 (eCTD 0002) on October 22, 2018.

Reference	Date	Title
(b) (4) Protocol	2016-JAN-05	Protocol for Systematic Literature Review for Trace Elements in Parenteral Nutrition, Prepared by (b) (4) for Luitpold
(b) (4) Report - Pediatric	2016-JUN-10	Systematic Literature Review for Trace Elements in Parenteral Nutrition: Zinc in the Pediatric Population, Prepared by (b) (4) for Luitpold
(b) (4) Report - Adults	2016-JUN-10	Systematic Literature Review for Trace Elements in Parenteral Nutrition: Zinc in the Adult Population, Prepared by (b) (4) for Luitpold
Clinical Overview - Adult	2017-OCT-14	Clinical Overview for Trace Element Injection (Adult), submitted as clinical-overview-1.pdf
Clinical Overview - Pediatric	2017-OCT-14	Clinical Overview for Trace Element Injection (Pediatric), submitted as clinical-overview-2.pdf
SCS - Adult	2017-OCT-14	Summary of Clinical Safety for Trace Element Injection (Adult), submitted as summary-clin-safety-1.pdf
SCS - Pediatric	2017-OCT-14	Summary of Clinical Safety for Trace Element Injection (Pediatric), submitted as summary-clin-safety-2.pdf

## 3. REVIEW RESULTS

### 3.1 A.S.P.E.N.

Partly informed by a 2009 review by Jeejeebhoy [2], the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) advocated in a 2015 Special Report for parenteral trace element products that include zinc, dosed at 3-5 mg/day for adults, 0.1 mg/kg/day for term infants and children, and 0.3 mg/kg/day for preterm infants [3]. The Special Report presented these doses as aligned with a 2012 A.S.P.E.N. Position Paper [4]. Regarding zinc for parenteral nutrition, the Position Paper recommended no change to clinical practice guidelines from 1979 [5, 6].

Jeejeebhoy identified a “syndrome comparable to acrodermatitis enteropathica” (skin parakeratosis and diarrhea) as an indicator for severe zinc deficiency during parenteral nutrition. Jeejeebhoy assessed risks of toxicity from parenteral zinc as “extremely small.” During normal enteral nutrition, according to Jeejeebhoy, fecal losses regulate plasma zinc levels to

concentrations between 80 and 120 µg/dL (*i.e.*, 12 and 18 µmol/L).<sup>d</sup> Nevertheless, Jeejeebhoy identified “no reliable way of assessing zinc status” during parenteral nutrition and described maintaining normal zinc status during parenteral nutrition as “more the art of medicine than science.”

Citing studies published before 1980, Jeejeebhoy identified (1) 2.5 mg/day as the parenteral zinc intake needed to maintain balance in adults without diarrhea [7], (2) 0.3-0.5 mg/kg/day as the parenteral zinc intake needed to maintain balance in infants [8], and (3) 0.1 mg/kg/day as a safe parenteral zinc intake sufficient for growth in older children [9].

For adults, Jeejeebhoy recommended parenteral zinc dosing at 3-4 mg/day, with 12 mg added for every liter of intestinal fluid loss.

### 3.2 Literature search by (b) (4)

#### 3.2.1 Methods

In January 2016, (b) (4) searched PubMed, EMBASE, and Cochran Reviews for full-text articles publishing results from original human research about (1) trace elements given parenterally or (2) trace-element status during parenteral nutrition. Stepped procedures for selecting articles included, (1) title screen with 25% quality control, (2) abstract screen with 25% quality control, and (3) full-text screen with 100% quality control. Finally, (b) (4) abstracted eligible articles for (1) patient population (adult or pediatric), (2) study design (randomized controlled trial, prospective cohort, retrospective cohort, case-control study, case series, and case report), (3) trace elements studied (chromium, copper, manganese, selenium, and zinc), (4) clinical setting (nutritional deficiency or nutritional support), and (5) study endpoint (laboratory or clinical).

#### 3.2.2 Results

(b) (4) identified 100 articles containing information about (1) patients given zinc parenterally or (2) zinc status in patients on parenteral nutrition. The (b) (4) list included 69 articles in adults [7, 10-77] and 31 articles in children [78-108]. According to (b) (4) eight articles addressed clinical endpoints in patients provided nutritional support with parenteral zinc at the exclusion of other trace elements [40, 71, 72, 74, 78, 82, 104, 105]. Table 1 summarizes the 100 (b) (4) articles by study population (adult or pediatric), study design, and trace element represented.

Table 1: (b) (4) articles about zinc, article counts, by study population, study design, and trace element.

Study Population Study Design	Zinc alone	Zinc and other trace elements	Zinc alone or together with other TEs
Adult			
Case series	10	21	31
Observational study	4	26	30

<sup>d</sup> Shown in Jeejeebhoy as 80 and 120 µg/L, assessed by DEPI as a typographical error in Jeejeebhoy.

Study Population Study Design	Zinc alone	Zinc and other trace elements	Zinc alone or together with other TEs
Randomized controlled trial	1	7	8
All study designs	15	54	69
<b>Pediatric</b>			
Case series	9	9	18
Observational study	2	11	13
Randomized controlled trial	0	0	0
All study designs	11	20	31
<b>Adult and pediatric</b>			
Case series	19	30	49
Observational study	6	37	43
Randomized controlled trial	1	7	8
All study designs	26	74	100

ABBREVIATIONS: (b) (4) TE, trace element

SOURCE: Table prepared by DEPI, combining Table 2 data from (b) (4) zinc reports for the adult and pediatric study populations.

FOOTNOTE: *Case series* includes articles classified as case series or case report by (b) (4). *Observational study* includes articles classified as clinical trial, prospective cohort, retrospective cohort, or case-control study by (b) (4).

### 3.2.3 DEPI overview of the clinical evidence from (b) (4)

DEPI assessed the 69 (b) (4) articles in adults, as follows,

- 20 articles principally about trace elements other than zinc [22, 25, 28, 30-32, 34, 36, 39, 42, 43, 45-48, 51, 54, 56, 57, 59].
- 7 articles from randomized studies of parenteral trace elements for preventing adverse outcomes in patients with acute life-threatening illness [17, 18, 23, 24, 33, 37, 49].
- 12 articles about clinical zinc deficiency in patients on parenteral nutrition [11, 12, 52, 60, 62, 64, 67, 70, 74-77].
- 1 article from an autopsy study measuring trace elements in tissues from eight patients who had received trace-element-supplemented parenteral nutrition for 2-21 years [19].
- 2 articles about inadvertent parenteral zinc overdose [69, 72].
- 16 articles from non-interventional studies in patients receiving parenteral nutrition, either short-term [10, 14, 16, 21, 26, 35, 41, 44] or long-term [13, 15, 20, 27, 29, 38, 58, 73].
- 11 articles from studies of controlled interventions involving zinc in patients on parenteral nutrition [7, 40, 50, 53, 55, 61, 63, 65, 66, 68, 71]. See **Section 3.2.4 Pivotal clinical studies** for narrative summaries of these articles.

DEPI assessed the 31 <sup>(b) (4)</sup> articles in children, as follows,

- 14 articles principally about trace elements other than zinc [79, 80, 83, 84, 86-89, 92-94, 96, 97, 101].
- 1 article from a randomized study of parenteral zinc for preventing adverse outcomes in children with acute life-threatening illness [78].
- 7 articles about clinical zinc deficiency in children on parenteral nutrition [81, 82, 90, 102-104, 106].
- 5 articles from non-interventional studies in children receiving parenteral nutrition, either short-term [91, 107] or long-term [85, 95, 108].<sup>e</sup>
- 4 articles from studies of controlled interventions involving zinc in children on parenteral nutrition [98-100, 105]. See **Section 3.2.4 Pivotal clinical studies** for narrative summaries of these articles.

### 3.2.4 Pivotal clinical studies

NDA 209377 seeks approval for zinc sulfate “as a source of zinc for parental nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.”<sup>f</sup> Accordingly, DEPI assessed the 100 articles from <sup>(b) (4)</sup> for clinical trial evidence, which might support a source-of-zinc indication, as proposed in NDA 209377. The following narratives summarize the best clinical trial evidence available, as assessed in DEPI.<sup>g</sup>

#### 3.2.4.1 Studies in adults

- **Messing 1977** [71]. In patients separated into two groups “according to sodium needs” and subsequently followed weekly for mean 38 days, investigators in Paris measured persistently low serum [Zn] ( $\leq 70$   $\mu\text{g/dL}$ ) in 1 of 15 (7%) and 3 of 5 (60%) patients on high-Zn (mean 4.26 mg/day) and low-Zn (0.54 mg/day) TPN, respectively.<sup>h</sup>
- **Wolman 1979** [7]. Investigators in Toronto studied zinc balance in 24 stable TPN-dependent patients, each followed over three consecutive one-week periods, with zinc supplementation (as Zn sulfate) during each study week, determined by randomization, at levels between 0.0

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<sup>e</sup> One article in this category provided information about a controlled intervention involving parenteral selenium [91].

<sup>f</sup> Prescribing Information for ZINC SULFATE INJECTION, USP for intravenous use after dilution, submitted to NDA 209377 (eCTD 0010) on February 14, 2019.

<sup>g</sup> Narratives use, as abbreviations or conventions, PN for parenteral nutrition, TPN for total parenteral nutrition, IV for parenteral, Zn for zinc, [Zn] for zinc concentration.

<sup>h</sup> Statistical significance of difference,  $p=0.032$ , Fisher’s exact test (2-sided), determined by DEPI using PROC FREQ in SAS 9.4.

and 3.0 mg/day (Group 1, N=17) or 6.0 and 23.0 mg/day (Group 2, N=7). Zinc natively present in TPN solutions provided an estimated zinc input of 1.0 mg/day. Eight of nine patients without significant diarrhea (stool weight <300 g/day) achieved positive zinc balance (*i.e.*, zinc intake > urinary and intestinal losses) when supplemented with zinc 3.0 mg/day. Investigators reported statistically significant association ( $p<0.001$ ) between plasma [Zn] and zinc dose (Figure 1).

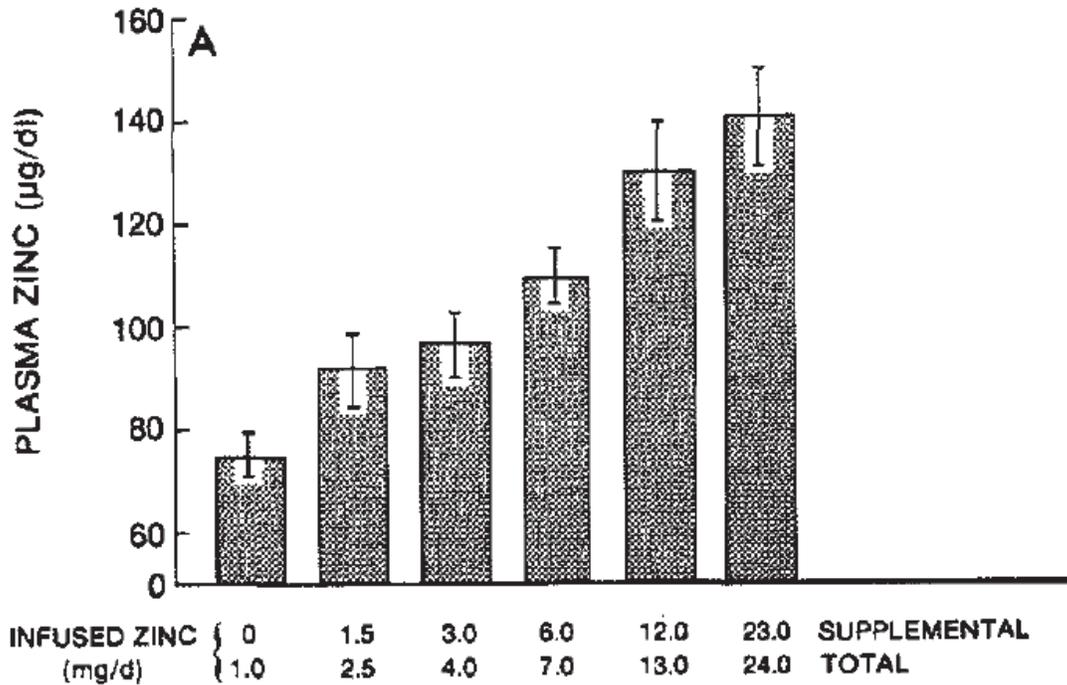


Figure 1: Association between plasma zinc concentration (mean  $\pm$  standard error) and parenteral zinc dose. Source: Figure 5 in Wolman 1979 [7].

- **Lowry 1979** [68]. In four cancer patients with weight loss and poor oral intake, investigators from the U.S. National Institutes of Health measured serum [Zn] before and after TPN with parenteral zinc. Serum [Zn] in one patient increased from 64 to 140  $\mu\text{g/dL}$  after 15 days of TPN with added zinc 2.67 mg/day.
- **Lowry 1981** [66]. Investigators from the U.S. National Institutes of Health measured serum [Zn] before and during 33 episodes of TPN in 24 patients with cancer. Twenty patients with 29 TPN episodes received supplemental zinc,  $\approx 4$  mg/day, as zinc chloride. Serum [Zn] during the first two weeks of TPN increased in patients supplemented with zinc and decreased in patients not supplemented with zinc (Figure 2).

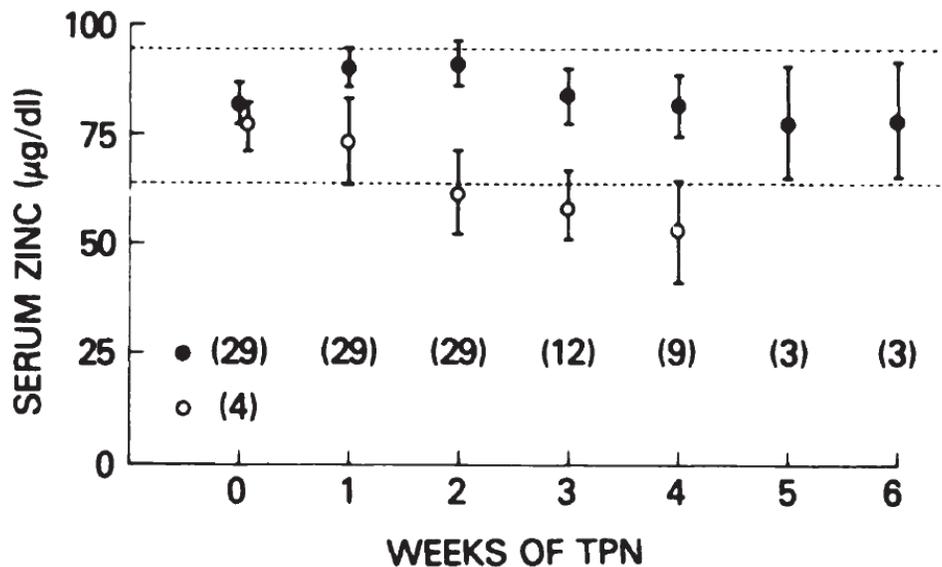


Figure 2: Serum zinc concentrations, mean  $\pm$  standard error, during episodes of TPN with (solid symbols) and without supplemental zinc (open symbols).  
 Source: Figure 1 in Lowry 1981 [66].

- **Phillips 1981** [65]. Serum [Zn] increased in 7 of 8 critically ill patients in Australia after 7 days of TPN with added zinc 1.0-2.5 mg/day (Figure 3).

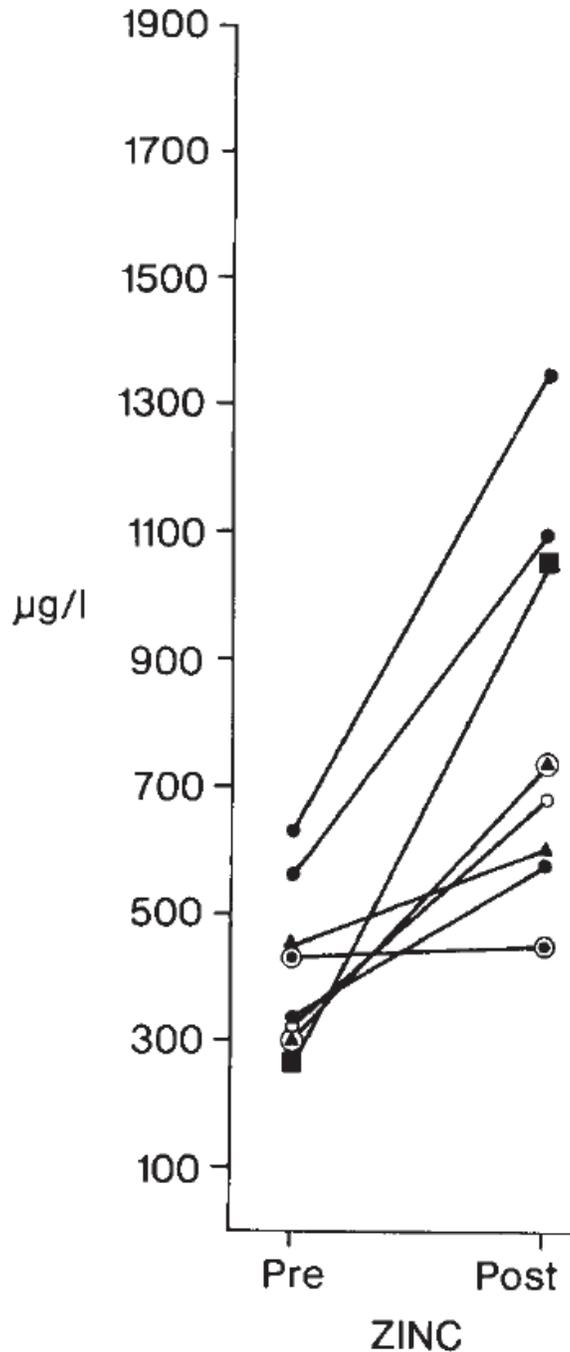


Figure 3: Serum zinc concentrations in eight critically ill patients before and after 7 days of TPN with added zinc 1.0-2.5 mg/day. Source: Figure 2 in Phillips 1981 [65].

- Main 1982** [63]. Investigators in Scotland measured serum [Zn] in 10 Crohn's disease patients before and after 14 episodes of TPN with trace metal solutions providing Zn 7.8 mg. The investigators reported "no relationship between the mean daily zinc supply and the overall changes in serum zinc concentration." Post-hoc analysis by DEPI showed parenteral

zinc increasing serum [Zn] in 1 of 5 patients supplemented at 2.7-6.5 mg/day and in 5 of 5 patients supplemented at 7.3-8.2 mg/day (Figure 4). Patients in the high-dose subgroup, however, started treatment with lower baseline serum [Zn].

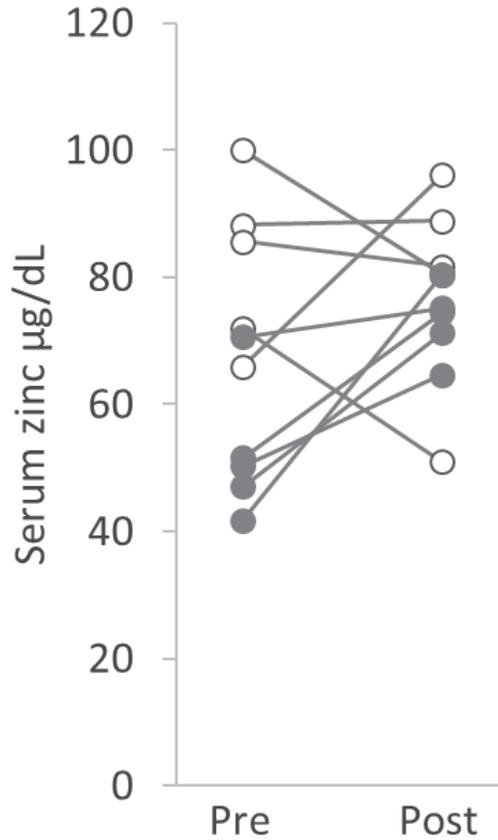


Figure 4: Serum zinc concentrations in 10 Crohn's disease patients before and after first episodes of TPN with zinc added at either 2.7-6.5 mg/day for 14-53 days (open symbols) or 7.3-8.2 mg/day for 27-42 days (solid symbols). Source: Plot prepared by DEPI from raw data in Main 1982 [63].

- **Jacobson 1984** [61]. Investigators in Sweden reported whole blood [Zn] as “unchanged throughout the period of TPN” in six Crohn's disease patients prescribed parenteral zinc 1.2-2.0 mg/day for 54-79 days.
- **Shenkin 1987** [55]. Investigators in Scotland measured mean serum [Zn] at 77 and 86 µg/dL in 22 post-surgical patients before and after 7-11 days of TPN with added Zn 6.5 mg/day.
- **Malone 1989** [53]. Investigators in Scotland measured serum [Zn] in 24 patients on long-term TPN (5-95 months) before and 1-14 months after switch to a new trace-element product. TPN provided mean Zn 4.1 and 4.8 mg/day before and after switch, respectively. Analyses showed “no major alterations in serum zinc status,” with mean serum [Zn]

measured at 86 and 90  $\mu\text{g/dL}$  before and after switch.

- **Chen 1991** [50]. Investigators in Taiwan randomized 17 patients (13 with cancer) to short-term TPN with no zinc (10 episodes in 9 patients) or zinc 0.68 mg per liter (8 patients). Mean serum [Zn] decreased significantly in patients after 4 weeks on TPN without zinc, but not in patients on TPN with zinc (Figure 5).

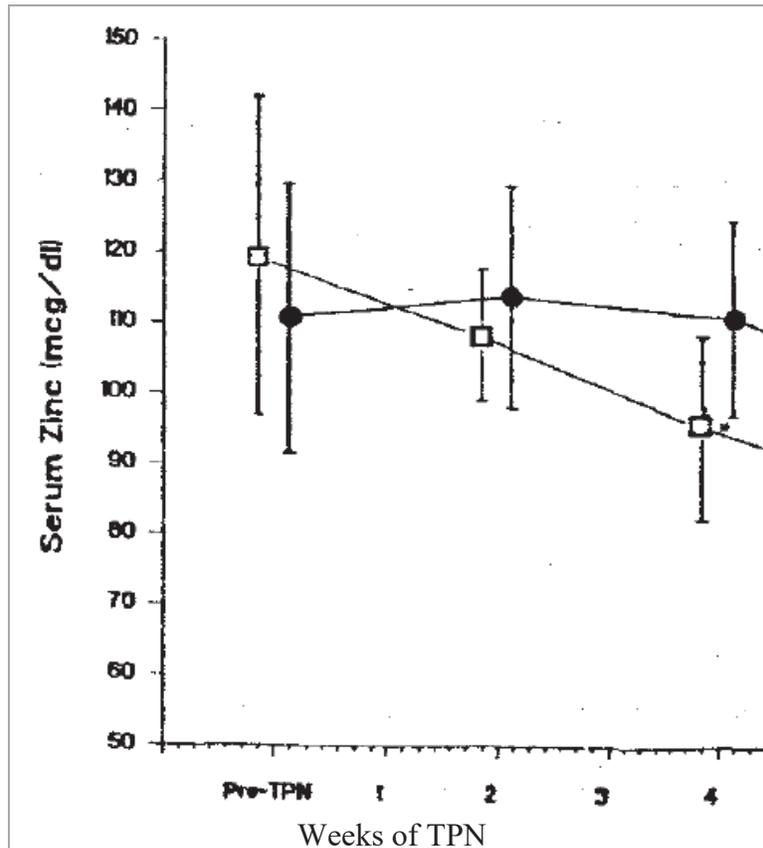


Figure 5: Serum zinc concentrations, mean  $\pm$  standard deviation, during a randomized clinical trial of TPN with (solid symbols) and without (open symbols) parenteral zinc supplementation. Source: Figure 1 in Chen 1991 [50].

- **Young 1996** [40]. Investigators in Kentucky randomized 68 patients with severe head trauma to up to 15 days of TPN with either standard-dose (2.5 mg/day; N=35) or high-dose zinc (8-12 mg/day; N=33). Both groups subsequently received enteral zinc, 22 mg/day, as zinc gluconate. Serum [Zn], low at baseline, increased comparably in standard- and high-dose groups (Figure 6).

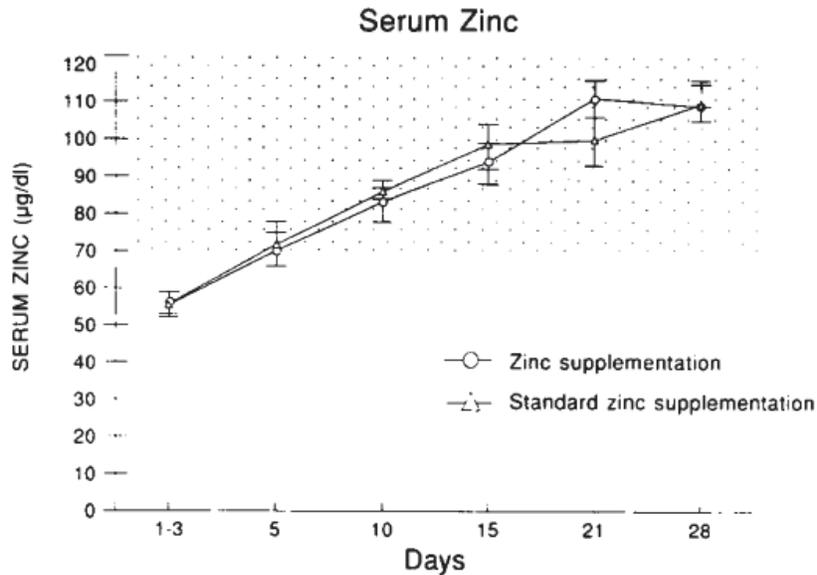


Figure 6: Mean serum zinc concentrations during a randomized clinical trial of supplemental zinc during TPN in patients with severe head trauma. Source: Figure 4 in Young 1996 [40].

#### 3.2.4.1 Studies in children

- Vileisis 1981** [105]. Investigators in Chicago randomized preterm infants, 1000-1500 gm birthweight, to two groups, (1) enteral feeding for four weeks (N=9) or (2) zinc-supplement-free parenteral feeding for two weeks followed by rapid weaning to enteral feeding for two additional weeks (N=8). Zinc intakes during enteral and parenteral feedings averaged 1.0 mg/kg/day and 0.046 mg/kg/day, respectively. Serum [Zn] declined in both groups (Figure 7).

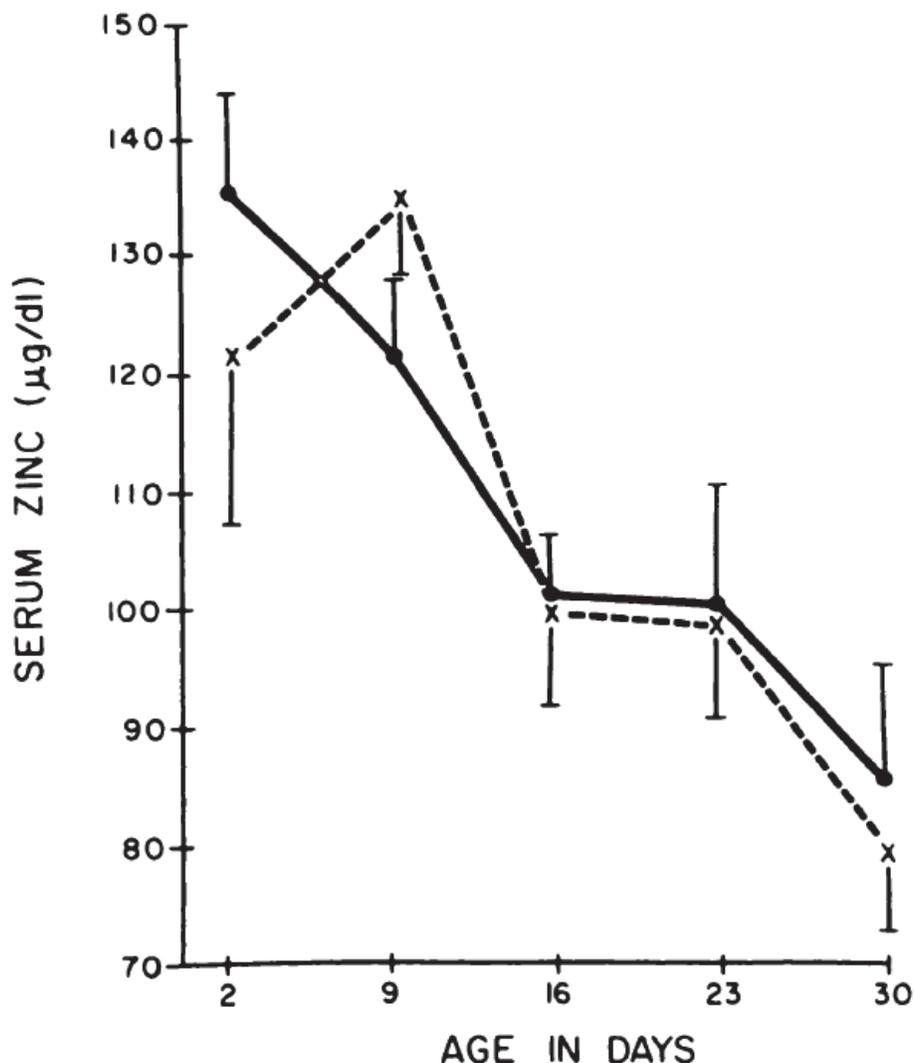


Figure 7: Serum zinc concentrations (mean  $\pm$  standard error) in preterm infants during a randomized clinical trial of enteral (X-symbols) vs. parenteral feeding (●-symbols). Source: Figure 1 in Vileisis 1981 [105].

- Suita 1984** [100]. Investigators in Japan randomized post-surgical newborn infants (12 full-term, 10 premature) to TPN with zinc 0.040 mg/kg/day added after (1) four weeks on TPN (N=10; total duration of TPN, median 43.5 days, range 21-223 days) or (2) one week on TPN (N=12; total duration of TPN, median 54.5 days, range 22-576 days). Clinical zinc deficiency developed in 3 of 10 (30%) and 2 of 12 (17%) infants from delayed and early zinc supplementation groups, respectively.<sup>i</sup> Case-based analysis indicated that TPN supplemented with zinc 0.04 mg/kg/day might not prevent deficiency in infants born prematurely or in infants losing intestinal fluids. After four weeks on zinc-supplemented TPN, some full-term infants had high serum [Zn] (up to 270  $\mu$ g/dL) without clinical evidence

<sup>i</sup> Statistical significance of difference,  $p=0.62$ , Fisher's exact test (2-sided), determined by DEPI using PROC FREQ in SAS 9.4.

for toxicity.

- **Friel 1984** [99]. Investigators in Ontario studied preterm infants provided (1) enteral feeding exclusively (N=15; mean birthweight 1291 gm) or (2) zinc-supplemented (0.35 mg/kg/day as zinc sulfate) total or partial parenteral nutrition (N=22; mean birthweight 909 gm; mean duration of parenteral nutrition 3 weeks). Over the first four weeks of life, mean serum [Zn] ( $\approx 130 \mu\text{g/dL}$  at birth) decreased by 30-40% and 15-20% in enterally and parenterally fed infants, respectively.
- **Lockitch 1985** [98]. Investigators in British Columbia randomized N=127 low birthweight infants (<2500 gm) to TPN regimens providing zinc 0.04, 0.1, 0.2, or 0.4 mg/kg/day and copper 20 or 40  $\mu\text{g/kg/day}$ . An earlier publication from the same trial reported declining mean serum [Zn] over the first two weeks of TPN in all zinc groups, except the zinc group supplemented at 0.4 mg/kg/day [109]. The investigators were “unable to show a lower incidence of [dermatitis] in the higher [zinc] supplement groups” [98].

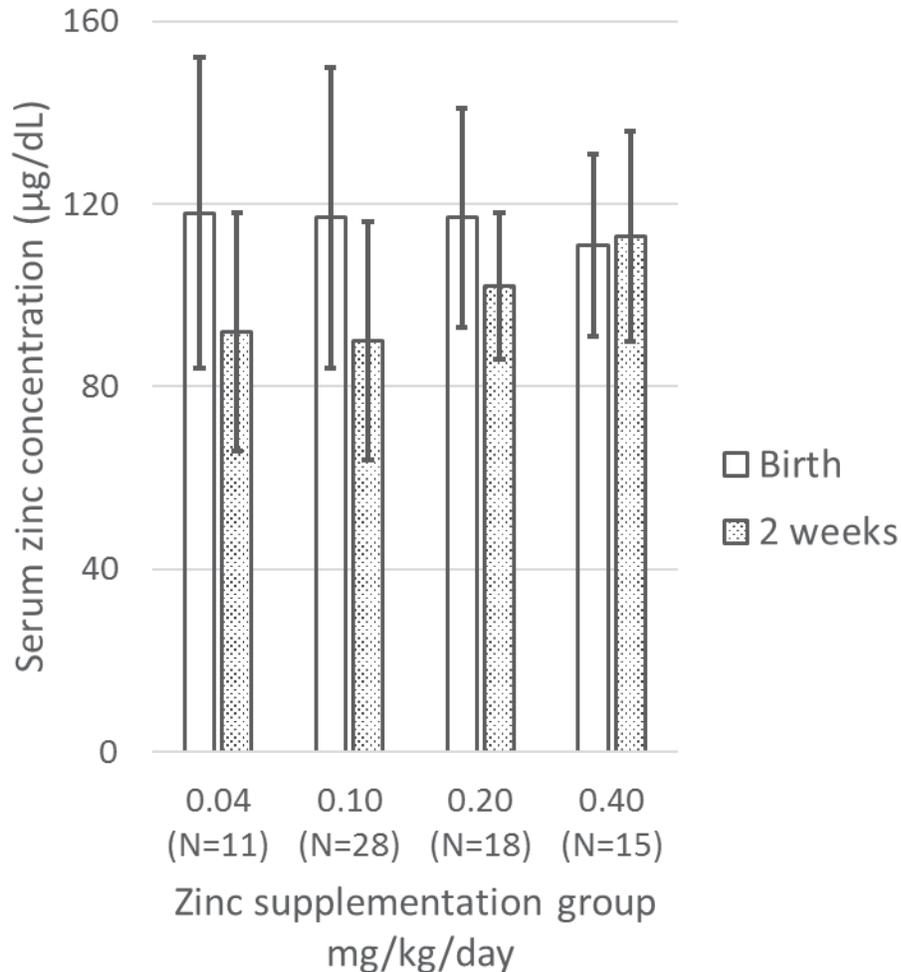


Figure 8: Serum zinc concentrations (mean  $\pm$  standard deviation) in low birthweight infants at birth and after two weeks of TPN supplemented with zinc

at 0.04, 0.10, 0.20, or 0.40 mg/kg/day. Source: Plot prepared by DEPI from summary data in Lockitch 1983 [109].

### 3.3 Safety evaluation by Luitpold

Luitpold assessed the 100 articles identified by (b) (4) for evidence about the safety or efficacy of parenteral zinc. Luitpold excluded from discussion (1) an autopsy study [19] and (2) 20 adult [22, 25, 28, 30-32, 34, 36, 39, 42, 43, 45-48, 51, 54, 56, 57, 59] and 14 pediatric articles [79, 80, 83, 84, 86-89, 92-94, 96, 97, 101], which primarily concerned trace elements other than zinc. Luitpold extracted and summarized safety and efficacy data from the 65 articles that remained [7, 10-18, 20, 21, 23, 24, 26, 27, 29, 33, 35, 37, 38, 40, 41, 44, 49, 50, 52, 53, 55, 58, 60-78, 81, 82, 85, 90, 91, 95, 98-100, 102-108]. An analysis of these 65 articles by Luitpold found six adult [10, 33, 37, 63, 69, 72] and three pediatric articles [78, 81, 100] that contained information about the toxicity or safety of parenteral zinc.<sup>j</sup> Luitpold found “no signal of zinc toxicity” in the six articles with safety information from controlled studies in adults [10, 33, 37, 63] or children [78, 100].<sup>k</sup>

### 3.4 Literature search by DEPI

To supplement the (b) (4) search, DEPI searched PubMed, Web of Science Core Collection, and article reference lists to identify 57 full-text articles publishing results from original research (1) in patients given zinc parenterally or (2) about zinc status in patients on parenteral nutrition (**APPENDIX 3**). DEPI’s supplemental search identified (1) the four (b) (4) articles published in 2015 [10-12, 78], (2) 34 other articles published in 2015 or later [110-143], and (3) 19 pre-2015 articles not captured by (b) (4) [8, 9, 109, 144-159]. Table 2 summarizes articles in the latter two categories.

Table 2: Articles contributed by DEPI, showing article counts, by study design and study population [1].

Study Design [2]	Study Population [3]		ALL
	Adult	Pediatric	
Case report	19	5	24
Descriptive	10	8	18
Non-randomized	4	3	7
Randomized	0	2	2
ALL	33	18	51

FOOTNOTES:

1. Article counts exclude duplicate reports — Reference [158] duplicates Reference [157] and Reference [155] duplicates Reference [154].
2. Non-randomized and randomized study designs compared outcomes between groups dosed differently with zinc.
3. The Adult column for Study Population includes three articles about both

<sup>j</sup> SCS - Adult, pp 9-10; SCS – Pediatric, pp 8-9.

<sup>k</sup> Clinical Overview - Adult, p 36.

adults and children [156, 157, 159].

### 3.5 Articles identified by DEPI, but not (b) (4)

DEPI identified 19 articles, from 17 studies, published before 2015, but not captured by (b) (4)

DEPI identified 18 case reports of zinc deficiency in patients on parenteral nutrition (Table 3). The four cases reported by Bos 1976 [153] included one instance of acute toxicity (sweating, rapid heart rate, blurred vision, low body temperature, and elevated serum [Zn] measured at 207 µg/dL) on the fourth day of 10 mg parenteral zinc administered as zinc sulfate over one hour. This patient subsequently tolerated the same zinc dose when administered over eight hours.

Table 3: Case reports, published before 2015, about zinc deficiency in patients on parenteral nutrition.

Author Year	Population	Location	N	Short Description
Franck 2014 [144]	Adult	U.S.	1	Low serum [Zn] attributed to drug shortage
Chun 2011 [145]	Pediatric	Korea	1	Bullous acrodermatitis enteropathica attributed to Zn deficiency
Serrano Ortega 1985 [149]	Adult	Spain	2	Dermatitis attributed to Zn deficiency
Brazin 1979 [151]	Pediatric	U.S.	1	Acrodermatitis enteropathica attributed to Zn deficiency
McCarthy 1978 [152]	Pediatric	U.S.	1	Dermatitis attributed to Zn deficiency
Bos 1976 [153]	Adult	Netherlands	4	Dermatitis attributed to Zn deficiency
Okada 1976 [157, 158]	Both	Japan	6	Dermatitis attributed to Zn deficiency
Arakawa 1976 [154, 155]	Pediatric	Japan	2	Dermatitis attributed to Zn deficiency

ABBREVIATIONS: N, patient count; Zn, zinc

DEPI identified five studies that described zinc status during parenteral nutrition (Table 4).

Table 4: Descriptive studies, published before 2015, about zinc status during parenteral nutrition.

Author Year	Population	Location	N	Short Description
Shulman 1989 [146]	Pediatric	U.S.	13	Results from TE balance studies in infants on PN
Tulikoura 1986 [147]	Adult	Finland	24	TE status assessed during TE-supplemented PN (See FOOTNOTE)
Solomons 1976 [159]	Both	U.S.	13	TE status assessed during PN
James 1976 [8]	Pediatric	Australia	4	Results from TE balance studies in premature infants on PN
Hankins 1976 [156]	Both	U.S.	8	TE status assessed during PN

ABBREVIATIONS: N, patient count; PN, parenteral nutrition; TE, trace element; Zn, zinc

FOOTNOTE: Tulikoura 1986 [147] assigned 24 adults to three different PN programs, with calories provided as (1) carbohydrate predominantly (91% of total calories; N=8), (2) lipids predominantly (51% of total calories; N=8), or (3) carbohydrate and amino acids (100% of total calories; N=8). All patients received the same amount of zinc in PN (1.9 mg/day).

DEPI identified two non-randomized studies of outcomes in patients on parenteral nutrition containing variable amounts of zinc (Table 5). Narrative summaries follow.

- **Jiang 1985** [148]. Between 1980 and 1983, investigators in China followed 25 gastrectomy patients on parenteral nutrition containing either zinc (initially 26 mg/day for three days, then 3 mg/day for five days; N=7) or no zinc (N=18). The investigators found that high-dose zinc “could not prevent the abrupt [post-operative] dip in serum zinc level” (Figure 9).

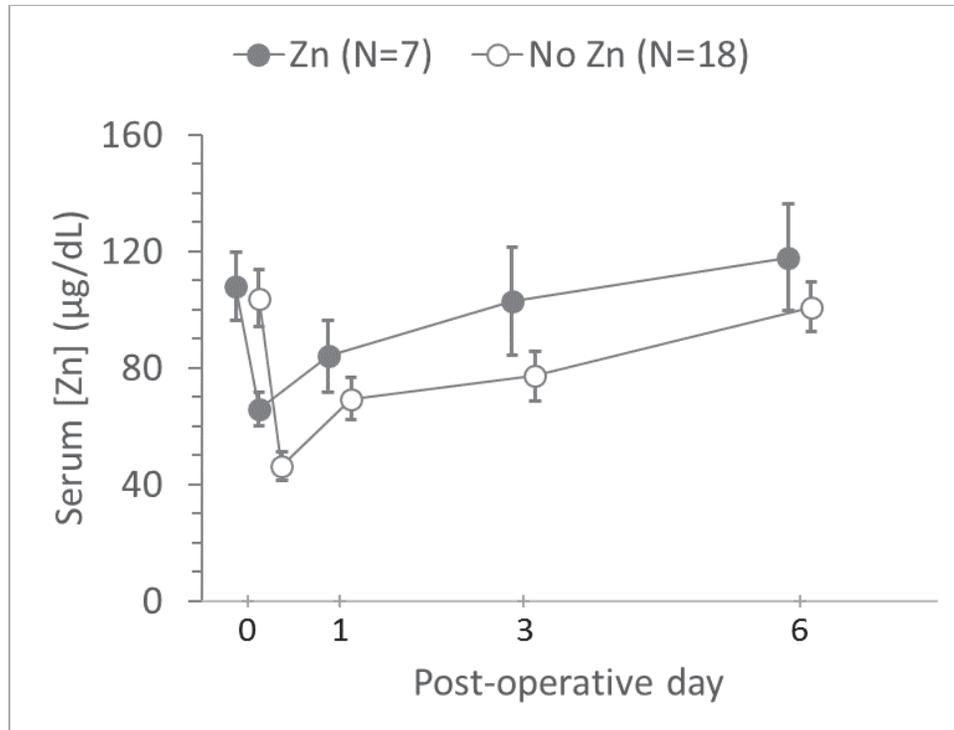


Figure 9: Serum zinc concentrations, mean and 95% confidence interval, in gastrectomy patients on parenteral nutrition with and without added zinc.

Source: Plot prepared by DEPI from summary data in Jiang 1985 [148].

- **Ricour 1977** [9]. Reporting in French, investigators in France followed eight infants and two children (age 2 and 8 years) starting parenteral nutrition that provided zinc dosed at either 0.03 or 0.05 mg/kg/day. The investigators found that neither dose prevented zinc depletion in plasma (Figure 10).

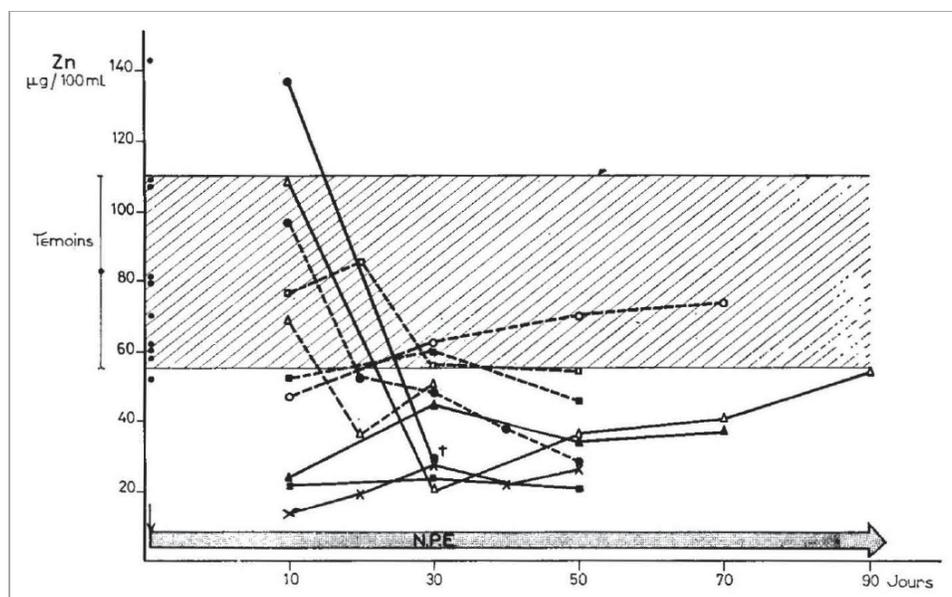


Figure 10: Plasma zinc concentrations in 10 pediatric patients during parenteral nutrition containing zinc dosed at 0.03 mg/kg/day (unbroken line, N=5) or 0.05 mg/kg/day (broken line; N=5). The hatched space identifies a normal range, as defined by 10 well-nourished children without digestive disease. Source: Figure 2 in Ricour 1977 [9]. (Note: Plot misplaced in source manuscript.)

Table 5: Non-randomized studies, published before 2015, about outcomes in patients on parenteral nutrition containing variable amounts of zinc.

Author Year	Population	Location	N <sub>1</sub>	N <sub>0</sub>	Short Description
Jiang 1985 [148]	Adult	China	7	18	Serum [Zn] assessed in surgical patients managed with and without IV Zn
Ricour 1977 [9]	Pediatric	France	5	5	TE status assessed during TE-supplemented PN

ABBREVIATIONS: N<sub>1</sub>, patients exposed or exposed at higher dose; N<sub>0</sub>, patients not exposed or exposed at lower dose; TE, trace element; Zn, zinc

DEPI identified two randomized studies of outcomes in infants on parenteral nutrition containing variable amounts of zinc (Table 6). <sup>(b) (4)</sup> identified and Luitpold summarized a 1985 derivative article [98] from a randomized study first reported in 1983 [109]. See **Lockitch 1985**, in Section 3.2.4.1 Studies in children, for a DEPI summary of this randomized study. A narrative summary of the second study follows.

- **Zlotkin 1983** [150]. Investigators in Ontario:
  - Randomly assigned 15 premature and 23 full-term infants without diarrhea to 6-day exclusive parenteral nutrition containing zinc dosed at either 0.14, 0.29, or 0.49 mg/kg/day.
  - Directly measured zinc in urine, stool, and nasogastric aspirate.
  - Estimated the linear association between the amounts of zinc administered by parenteral

nutrition and the amounts of zinc retained (*i.e.*, the difference between zinc administered and zinc lost), with both amounts calculated as daily averages over the last three days of parenteral nutrition.

- Estimated 0.15 mg/kg/day as the minimum zinc dose needed by infants to replace zinc normally lost in urine and stool.
- Estimated 0.44 mg/kg/day as the zinc dose needed in premature infants to match zinc retention *in utero* (taken as 0.24 mg/kg/day).

Other results from **Zlotkin 1983** included,

- “Clinical outcomes unaffected by level of zinc ... supplementation.”
- “Toxic clinical effects ... not observed even at the highest levels of supplementation.”
- Plasma [Zn] “values ... unrelated to intake.”

Table 6: Randomized studies, published before 2015, about outcomes in infants on parenteral nutrient containing variable amounts of zinc.

Author Year	Population	Location	N	Short Description
Lockitch 1983 [109]	Pediatric	British Columbia	127	TE status assessed in low-birth-weight infants on PN containing Zn dosed at 0.04, 0.1, 0.2, or 0.4 mg/kg/day
Zlotkin 1983 [150]	Pediatric	Ontario	38	TE status assessed in infants on PN containing Zn dosed at 0.14, 0.29, or 0.49 mg/kg/day

ABBREVIATIONS: N, patient count; PN, parenteral nutrition; TE, trace element; Zn, zinc

### 3.6 Articles published in 2015 or later

DEPI identified 34 possibly informative articles published in 2015 or later [110-143].

DEPI identified 16 case reports about outcomes in (1) patients provided parenteral zinc or (2) patients assessed for zinc status during parenteral nutrition (Table 7). Seven case reports primarily concerned deficiencies or excesses related to trace elements other than zinc [113, 115, 120, 124, 126, 129, 133].

Table 7: Case reports, published in 2015 or later, about outcomes in (1) patients provided parenteral zinc or (2) patients assessed for zinc status during parenteral nutrition.

Author Year	Population	Location	Short Description
Jakubovic 2015 [112]	Adult	Ontario	Necrolytic acral erythema and coma post bariatric surgery in a Zn-deficient 34-year-old woman treated successfully with enteral and parenteral supplements

Author Year	Population	Location	Short Description
Prasad 2015 [113]	Adult	U.K.	A 65-year-old woman with Crohn's disease and PN-associated Cu deficiency attributed to Zn-containing dental adhesive
Vick 2015 [114]	Adult	U.S.	Perineal rash post bariatric surgery in a Zn- and Cu-deficient 38-year woman treated successfully with IV Zn and Cu
Avila 2016 [115]	Adult	U.S.	Zn status assessed in a 55-year-old man with celiac disease and PN-associated myopathy attributed to Cu deficiency
Maskarinec 2016 [119]	Adult	U.S.	A 50-year-old man with PN-associated acrodermatitis enteropathica attributed to Zn deficiency
Moser 2016 [120]	Pediatric	Germany	Zn status assessed in a 14-year-old boy with PN-associated pancytopenia attributed to Cu deficiency
Rana 2016 [121]	Adult	U.S.	Zn deficiency and acrodermatitis enteropathica post bariatric surgery in a 39-year-old woman treated with IV Zn
Sant 2016 [123]	Adult	U.S.	A 52-year-old man with PN-associated dermatitis attributed to Zn deficiency
Walter 2016 [124]	Adult	U.K.	High blood [Mn] in 62-year-old man on TE-supplemented PN
Zhu 2016 [125]	Adult	U.S.	A 47-year-old woman with bulimia, gastroparesis, and PN-associated acrodermatitis enteropathica attributed to Zn deficiency
Cavallieri 2017 [126]	Adult	Italy	Zn status assessed in a 60-year-old man treated with IV Cu for subacute myelopathy attributed to occult celiac disease and Cu deficiency
Okhovat 2017 [128]	Adult	U.S.	A 42-year-old woman with short bowel syndrome and PN-associated acrodermatitis enteropathica attributed to Zn deficiency
Oo 2017 [129]	Adult	U.S.	Zn status assessed in a 40-year-old woman on PN for two years with bone marrow changes attributed to Cu deficiency
Wazir 2017 [133]	Adult	U.S.	Zn status assessed in a 72-year-old woman treated with IV Cu for myeloneuropathy, leucopenia, anemia, and low serum [Cu] attributed to poor eating habits
Wu 2017 [134]	Adult	U.S.	A 69-year-old woman with ovarian cancer and PN-associated bullous acrodermatitis attributed to Zn deficiency
Baruch 2018 [136]	Adult	U.S.	A 54-year-old woman with PN-associated acrodermatitis enteropathica attributed to Zn deficiency

ABBREVIATIONS: Cu, copper; IV, intravenous; PN, parenteral nutrition; N, patient count; Mn, manganese; TE, trace element; Zn, zinc

DEPI identified 13 articles that described (1) zinc status in patients provided parenteral zinc or (2) other outcomes during zinc-supplemented parenteral nutrition (Table 8). Three articles documented patient exposures to zinc by amount.

- **Dastyh 2016** [117]. In 68 adults on long-term PN (4-96 months) for short bowel syndrome, investigators in the Czech Republic measured mean serum [Zn] at 84 µg/dL, interquartile range, IQR, 69-110 µg/dL, with parenteral zinc exposure over the previous three months estimated at 4.6 mg/day, IQR 2.8-6.5 mg/day.
- **Uzzan 2017** [131]. In 71 adults on stable long-term PN (mean 8.9 years), investigators in France measured mean serum [Zn] at 118 µg/dL, standard deviation, SD, 44 µg/dL, with parenteral zinc exposure estimated at mean 9.4 mg/day, SD 5.7 mg/day. In 31 (44%) patients, serum [Zn] exceeded the upper limit of the reference range (118 µg/dL).
- **Lin 2018** [141]. Investigators in Taiwan reported “no adverse effects” from treating two postherpetic neuralgia patients with IV zinc (as Zn sulfate) 35 mg every other day for 6 or 8 doses.

Table 8: Descriptive studies, published in 2015 or later, about (1) zinc status in patients provided parenteral nutrition or (2) other outcomes during zinc-supplemented parenteral nutrition.

Author Year	Population	Location	N	Short Description
Dastyh 2016 [116]	Adult	Czech Republic	16	Mn status assessed during TE-supplemented PN
Dastyh 2016 [117]	Adult	Czech Republic	68	TE status assessed during TE-supplemented PN
Greene 2016 [118]	Pediatric	U.K.	36	Mn status assessed during TE-supplemented PN
Salota 2016 [122]	Adult	U.K.	166	Associations between C-reactive protein and serum TE concentrations during TE-supplemented PN
Namjoshi 2017 [127]	Pediatric	U.S.	60	TE status assessed during TE-supplemented PN
Theilla 2017 [130]	Adult	Israel and Poland	7	Outcomes from 9 pregnancies in 7 women on TE-supplemented PN during pregnancy
Uzzan 2017 [131]	Adult	France	71	TE status and serious infection assessed during PN
Van Gossum 2017 [132]	Adult	Europe	77	TE status assessed during PN in patients with complications from bariatric surgery
Yanagisawa 2017 [135]	Pediatric	Japan	22	Zn status assessed in children on PN during hematopoietic stem cell transplantation
Dressler 2018 [138]	Pediatric	Austria	17	Outcomes assessed in children on TE-supplemented ketogenic PN for seizure control

Author Year	Population	Location	N	Short Description
Gupta 2018 [139]	Pediatric	U.S.	24	Cu status assessed in premature infants with PN-associated cholestasis
Lin 2018 [141]	Adult	Taiwan	2	Open-label trial of IV Zn for postherpetic neuralgia
Neelis 2018 [142]	Pediatric	Netherlands	52	Nutritional status assessed during TE-supplemented PN

ABBREVIATIONS: Cu, copper; IV, intravenous; Mn, manganese; PN, parenteral nutrition; TE, trace element; Zn, zinc

Five articles reported results from non-randomized studies in patients with varied exposure to parenteral zinc (Table 9). Narrative summaries follow.

- **Aschner 2015** [110]. Investigators in Tennessee used brain magnetic resonance imaging to assess manganese toxicity in 58 infants, including 39 and 19 infants with high and low exposure to parenteral nutrition (approximated by >21 vs. <14 days of total parenteral nutrition), respectively, with trace elements (including zinc) provided by adding 0.2 mL of Multitrace-4 neonatal to every 100 mL of parenteral nutrition solution.
- **Braga 2015** [111]. Investigators in Brazil assessed serum [Zn] in 22 adults with short bowel syndrome, including 11 adults who required intermittent parenteral nutrition provided in hospital every 10-40 days for 3-8 days. Parenteral nutrition provided zinc 2.5 mg/day.
- **Capone 2018** [137]. Investigators in Chicago assessed glucose control in 348 and 358 infants during the first week of parenteral nutrition providing zinc 0.5 and 0.3 mg/kg/day, respectively.
- **Jafari 2018** [140]. Investigators in Switzerland assessed serum [Zn] in 15 burn patients, including 7 patients intravenously administered Zn 47.5 mg/day, with other trace elements, for up to 30 days.
- **Rehou 2018** [143]. Investigators in Canada assessed clinical outcomes in 172 burn patients, including 81 patients intravenously administered Zn 30 mg/day, with other trace elements, for up to 14 days. Death occurred more frequently in patients administered trace elements, 14 of 81 (17%) vs. 9 of 91 (10%), p=0.18.

Table 9: Non-randomized studies, published in 2015 or later, in patients with varied exposure to parenteral zinc.

Author Year	Population	Location	N	Target Population
Aschner 2015 [110]	Pediatric	U.S.	58	Newborns in ICU
Braga 2015 [111]	Adult	Brazil	22	Short bowel syndrome
Capone 2018 [137]	Pediatric	U.S.	706	Newborns in ICU
Jafari 2018 [140]	Adult	Switzerland	15	Burn patients admitted to ICU
Rehou 2018 [143]	Adult	Canada	172	Burn patients admitted to ICU

ABBREVIATIONS: ICU, intensive care unit, N, patient count

### 3.7 Quality check on safety reporting

DEPI verified Luitpold's safety presentation for six articles, which contained, according to Luitpold, safety results from controlled studies with N=127 adults [10, 33, 37, 63] and N=36 children [78, 100] exposed to parenteral zinc. To identify useful safety data possibly overlooked by Luitpold, DEPI scanned the 100 articles identified by (b) (4) for specific data or declarations about the presence or absence of toxicities, complications, side effects, or adverse events during exposure to parenteral zinc. This scan identified 20 articles from 19 studies, including three case reports [72, 76, 81], five descriptive studies [15, 16, 61, 63, 69], and ten controlled studies [10, 17, 23, 33, 37, 49, 50, 78, 84, 100]. Despite scattered reports of elevated zinc concentrations in blood [15, 78, 100], DEPI found no clear evidence in these 20 articles for serious adverse events attributable to parenteral zinc when properly dosed. See **APPENDIX 5** for details.

Two articles provided information about the consequences of zinc overdose.

- **Brocks 1977** [72]. A 72-year-old woman with Crohn's disease suffered acute intoxication, resulting in death, after inadvertent overdose with parenteral zinc (1200 mg/day for 2.5 days).
- **Faintuch 1978** [69]. Seven patients (16 to 41 years in age) received parenteral nutrition inadvertently overdosed with zinc (50-75 mg/day for mean 46 days, range 26-60 days), resulting in serum zinc concentrations >310 µg/dL. Subsequent follow-up in six patients documented high blood amylase concentrations, with peak levels reaching 1.8-6.0 times the upper limit of normal.

The Luitpold safety presentation excluded an autopsy study.

- **Howard 2007** [19]. Investigators measured trace elements in heart, muscle, kidney, and liver from eight autopsy patients (age at death, 29-78 years) who had received long-term (>2 years) parenteral nutrition, discontinued no earlier than four weeks before death. Patients had received zinc supplements according to local practice, 3 mg/day base, with 3-5 mg added for every liter of enteric fluid loss. Five patients had excess zinc measured in liver.

## 4. DISCUSSION

To support NDA 209377, which seeks FDA approval for zinc sulfate as a source of zinc for parenteral nutrition, the NDA sponsor (Luitpold) evaluated 100 articles found by systematic search for medical literature about (1) patients given zinc parenterally or (2) zinc status in patients on parenteral nutrition. Luitpold found "no signal of zinc toxicity" in 6 articles with safety information from controlled studies in adults.

(b) (4)

The Division and the Sponsor agreed on an approach, which required the Sponsor to (1) conduct a thorough and

(b) (4)

transparent search for clinical literature (b) (4) (2) standardize methods for extracting data about dosing, efficacy, and safety, and (3) organize data presentations in a prescribed manner conducive to FDA review.

Accordingly, Luitpold hired an independent entity (b) (4), which followed a protocol previously reviewed by DEPI to identify possibly informative articles in medical literature.<sup>m</sup> Subsequently, Luitpold used a tabular format recommended by DGIEP to extract information about dosing, efficacy, and safety from articles identified by (b) (4). Finally, Luitpold organized extracted information in a manner prescribed by DGIEP, with separate presentations for efficacy and safety in adult and pediatric populations. Therefore, upon examination of the clinical summaries and supporting documents submitted under NDA 209377, DEPI finds that Luitpold conducted a Systematic Literature Review, as stipulated by pre-NDA negotiations between DGIEP and Luitpold.

DEPI views the (b) (4) search as credibly conducted and the Luitpold safety assessment as responsibly reported, as established by quality checks summarized in **Section 3.7 Quality check on safety reporting** and supported by data tables in **APPENDIX 5**.

(b) (4) searched for literature published in 2015 or earlier. Applying the (b) (4) search strategy to PubMed, DEPI updated the (b) (4) search with 34 additional articles published in 2015 or later. In addition, DEPI augmented the (b) (4) search by targeting articles found by reference-list search. This reference-list search identified nineteen pre-2015 articles not captured by (b) (4). The additional articles identified by DEPI provided no new information that qualitatively changed DEPI's understanding of the safety of zinc for parenteral nutrition, as presented by Luitpold.

As suggested in its June 2016 Protocol Review, DEPI views systematic literature search as a transparent, conscientious, and accountable method for identifying safety signals in literature and possibly informing the safety sections in labels (b) (4). In this context, DEPI independently assessed the accumulated clinical literature for evidence about the safety of zinc for parenteral nutrition. Despite the typically absent, vague, or abbreviated presentation of safety results in published reports, DEPI found little practical concern expressed in literature about toxicity from parenteral zinc when dosed according to current conventions.

During pre-NDA negotiations, DGIEP suggested that Luitpold might use information in literature (b) (4) to support dosing recommendations (b) (4) when administered by a parenteral route, especially in special populations. Though not asked to do so, Luitpold commissioned a systematic literature review of enteral zinc supplementation. Because of the low bioavailability of enteral zinc, DEPI bypassed the

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(b) (4)

Luitpold-commissioned review of enteral zinc supplementation.

**Section 3.2.4 Pivotal clinical studies** summarizes some literature possibly used by clinical experts to justify conventional zinc dosing during parenteral nutrition. The DEPI search identified several possibly relevant articles overlooked by (b) (4) and Luitpold, particularly **Ricour 1977** [9], **Lockitch 1983** [109], and **Zlotkin 1983** [150]. DEPI alerts DGIEP about these articles, which might help inform FDA dose recommendations for parenteral zinc sulfate.

## 5. CONCLUSIONS

DEPI finds that,

- Luitpold conducted a Systematic Literature Review, as stipulated by pre-NDA negotiations between DGIEP and Luitpold.
- No evidence in medical literature for toxicity or other serious adverse consequences from zinc, when administered intravenously for parenteral nutrition at conventional doses.
- Additional articles found in literature by DEPI support Luitpold’s finding of “no signal of zinc toxicity” from zinc for parenteral nutrition.

## 6. RECOMMENDATIONS FOR DGIEP

DEPI identifies clinical studies that DGIEP might use to support dose recommendations for parenteral zinc sulfate.

## 7. REFERENCES

1. Institute of Medicine. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Washington, DC: The National Academy Press; 2006.
2. Jeejeebhoy K. Zinc: an essential trace element for parenteral nutrition. *Gastroenterology*. 2009 Nov;137(5 Suppl):S7-12.
3. 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 Aug;30(4):559-69.
4. 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 Aug;27(4):440-91.
5. Guidelines for essential trace element preparations for parenteral use. A statement by the Nutrition Advisory Group. American Medical Association. *JPEN J Parenter Enteral Nutr*. 1979 Jul-Aug;3(4):263-7.
6. Guidelines for essential trace element preparations for parenteral use. A statement by an expert panel. AMA Department of Foods and Nutrition. *JAMA*. 1979 May 11;241(19):2051-4.

7. Wolman SL, Anderson GH, Marliss EB, Jeejeebhoy KN. Zinc in total parenteral nutrition: Requirements and metabolic effects. *Gastroenterology*. 1979 Mar;76(3):458-67.
8. James BE, MacMahon RA. Balance studies of nine elements during complete intravenous feeding of small premature infants. *Aust Paediatr J*. 1976 Sep;12(3):154-62.
9. Ricour C, Duhamel JF, Gros J, Maziere B, Comar D. [Estimates of trace elements requirements of children receiving total parenteral nutrition]. *Arch Fr Pediatr*. 1977 Aug-Sep;34(7 Suppl):XCII-C.
10. Liu MY, Tang HC, Hu SH, Yang HL, Chang SJ. Influence of preoperative peripheral parenteral nutrition with micronutrients after colorectal cancer patients. *Biomed Res Int*. 2015;2015:535431.
11. 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 Nov;39(8):986-9.
12. Sidana S, Madanat Y, Pile J. Got zinc? An exfoliative rash in a parenteral nutrition-dependent patient. *J Gen Intern Med*. 2015 Apr;30(4):529-30.
13. Abdalian R, Fernandes G, Duerksen D, et al. Prescription of trace elements in adults on home parenteral nutrition: Current practice based on the Canadian Home Parenteral Nutrition Registry. *JPEN J Parenter Enteral Nutr*. 2013 May-Jun;37(3):410-5.
14. 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 Dec;150(1-3):109-15.
15. Btaiche IF, Carver PL, Welch KB. Dosing and monitoring of trace elements in long-term home parenteral nutrition patients. *JPEN J Parenter Enteral Nutr*. 2011 Nov;35(6):736-47.
16. Ishizuka M, Nagata H, Takagi K, Kubota K. Sequential evaluations of trace elements in patients receiving parenteral nutrition. *Hepatogastroenterology*. 2011 Sep-Oct;58(110-111):1466-9.
17. Berger MM, Baines M, Raffoul W, et al. Trace element supplementation after major burns modulates antioxidant status and clinical course by way of increased tissue trace element concentrations. *Am J Clin Nutr*. 2007 May;85(5):1293-300.
18. Berger MM, Binnert C, Chioloro RL, et al. Trace element supplementation after major burns increases burned skin trace element concentrations and modulates local protein metabolism but not whole-body substrate metabolism. *Am J Clin Nutr*. 2007 May;85(5):1301-6.
19. Howard L, Ashley C, Lyon D, Shenkin A. Autopsy tissue trace elements in 8 long-term parenteral nutrition patients who received the current U.S. Food and Drug Administration formulation. *JPEN J Parenter Enteral Nutr*. 2007 Sep-Oct;31(5):388-96.

20. Barrera R, Schattner M, Gabovich N, et al. Bacteremic episodes and copper/zinc ratio in patients receiving home parenteral nutrition. *Nutr Clin Pract*. 2003 Dec;18(6):529-32.
21. Papageorgiou T, Zacharoulis D, Xenos D, Androulakis G. Determination of trace elements (Cu, Zn, Mn, Pb) and magnesium by atomical absorption in patients receiving total parenteral nutrition. *Nutrition*. 2002 Jan;18(1):32-4.
22. Yusuf SW, Rehman Q, Casscells W. Cardiomyopathy in association with selenium deficiency: A case report. *JPEN J Parenter Enteral Nutr*. 2002 Jan-Feb;26(1):63-6.
23. Berger M, Baines M, Chioloro R, Wardle C, Cayeux C, A S. Influence of early trace element and vitamin E supplements on antioxidant status after major trauma: A controlled trial. *Nutr Res*. 2001;21:41-54.
24. Berger MM, Reymond MJ, Shenkin A, et al. Influence of selenium supplements on the post-traumatic alterations of the thyroid axis: A placebo-controlled trial. *Intensive Care Med*. 2001 Jan;27(1):91-100.
25. 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 Mar-Apr;25(2):87-92.
26. Orimo S, Ozawa E. Short-term administration of an essential trace elements preparation (Elemenic) causes a high whole blood manganese concentration and manganese deposition in basal ganglia. *Intern Med*. 2001 Nov;40(11):1162-3.
27. Reimund JM, Dietemann JL, Warter JM, Baumann R, Duclos B. Factors associated to hypermanganesemia in patients receiving home parenteral nutrition. *Clin Nutr*. 2000 Oct;19(5):343-8.
28. Fitzgerald K, Mikalunas V, Rubin H, McCarthey R, Vanagunas A, Craig RM. Hypermanganesemia in patients receiving total parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 1999 Nov-Dec;23(6):333-6.
29. Reimund J, Duclos B, Cuby C, et al. Home parenteral nutrition: clinical and laboratory analysis of initial experience (1994-1997). Implications for patient management. *Ann Nutr Metab*. 1999;43(6):329-38.
30. 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 Jan 1;162(1):102-5.
31. Spiegel JE, Willenbacher RF. Rapid development of severe copper deficiency in a patient with Crohn's disease receiving parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 1999 May-Jun;23(3):169-72.
32. 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(8):773-6.

33. Berger MM, Spertini F, Shenkin A, et al. Trace element supplementation modulates pulmonary infection rates after major burns: A double-blind, placebo-controlled trial. *Am J Clin Nutr*. 1998 Aug;68(2):365-71.
34. Reynolds N, Blumsohn A, Baxter JP, Houston G, Pennington CR. Manganese requirement and toxicity in patients on home parenteral nutrition. *Clin Nutr*. 1998 Oct;17(5):227-30.
35. Alfieri MA, Leung FY, Grace DM. Selenium and zinc levels in surgical patients receiving total parenteral nutrition. *Biol Trace Elem Res*. 1998 Jan;61(1):33-9.
36. Tsuda K, Yokoyama Y, Morita M, Nakazawa Y, Onishi S. Selenium and chromium deficiency during long-term home total parenteral nutrition in chronic idiopathic intestinal pseudoobstruction. *Nutrition*. 1998 Mar;14(3):291-5.
37. Braunschweig CL, Sowers M, Kovacevich DS, Hill GM, August DA. Parenteral zinc supplementation in adult humans during the acute phase response increases the febrile response. *J Nutr*. 1997 Jan;127(1):70-4.
38. Forbes GM, Forbes A. Micronutrient status in patients receiving home parenteral nutrition. *Nutrition*. 1997 Nov-Dec;13(11-12):941-4.
39. Alves G, Thiebot J, Tracqui A, Delangre T, Guedon C, Lerebours E. Neurologic disorders due to brain manganese deposition in a jaundiced patient receiving long-term parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 1997 Jan-Feb;21(1):41-5 ).
40. Young B, Ott L, Kasarskis E, et al. Zinc supplementation is associated with improved neurologic recovery rate and visceral protein levels of patients with severe closed head injury. *J Neurotrauma*. 1996 Jan;13(1):25-34.
41. Leung FY, Galbraith LV. Elevated serum chromium in patients on total parenteral nutrition and the ionic species of contaminant chromium. *Biol Trace Elem Res*. 1995 Dec;50(3):221-8.
42. Winnefeld K, Dawczynski H, Schirrmeister W, Adam G, Friedrich U, Hein S. Selenium in serum and whole blood in patients with surgical interventions. *Biol Trace Elem Res*. 1995 Nov;50(2):149-55.
43. Wasa M, Satani M, Tanano H, Nezu R, Takagi Y, Okada A. Copper deficiency with pancytopenia during total parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 1994 Mar-Apr;18(2):190-2.
44. Faure H, Leverve X, Arnaud J, Boujet C, Favier A. Zinc changes in blood and urine during cyclic parenteral nutrition: Relationships with amino acid metabolism. *Br J Nutr*. 1994 Nov;72(5):763-73.

45. Kawakubo K, Iida M, Matsumoto T, et al. Progressive encephalopathy in a Crohn's disease patient on long-term total parenteral nutrition: Possible relationship to selenium deficiency. *Postgrad Med J*. 1994 Mar;**70**(821):215-9.
46. Sando K, Hoki M, Nezu R, Takagi Y, Okada A. Platelet glutathione peroxidase activity in long-term total parenteral nutrition with and without selenium supplementation. *JPEN J Parenter Enteral Nutr*. 1992 Jan-Feb;**16**(1):54-8.
47. Mirowitz SA, Westrich TJ. Basal ganglial signal intensity alterations: Reversal after discontinuation of parenteral manganese administration. *Radiology*. 1992 Nov;**185**(2):535-6.
48. Abrams CK, Siram SM, Galsim C, Johnson-Hamilton H, Munford FL, Mezghebe H. Selenium deficiency in long-term total parenteral nutrition. *Nutr Clin Pract*. 1992 Aug;**7**(4):175-8.
49. Faure H, Peyrin JC, Richard MJ, Favier A. Parenteral supplementation with zinc in surgical patients corrects postoperative serum-zinc drop. *Biol Trace Elem Res*. 1991 Jul;**30**(1):37-45.
50. Chen W, Chiang TP, Chen TC. Serum zinc and copper during long-term total parenteral nutrition. *J Formos Med Assoc*. 1991 Nov;**90**(11):1075-80.
51. Mirowitz SA, Westrich TJ, Hirsch JD. Hyperintense basal ganglia on T1-weighted MR images in patients receiving parenteral nutrition. *Radiology*. 1991 Oct;**181**(1):117-20.
52. Chen W, Wong WK, Chen TC. A case of zinc deficiency during long-term total parenteral nutrition. *J Formos Med Assoc*. 1990 May;**89**(5):388-91.
53. Malone M, Shenkin A, Fell GS, Irving MH. Evaluation of a trace element preparation in patients receiving home intravenous nutrition. *Clin Nutr*. 1989 Dec;**8**(6):307-12.
54. Fujita M, Itakura T, Takagi Y, Okada A. Copper deficiency during total parenteral nutrition: Clinical analysis of three cases. *JPEN J Parenter Enteral Nutr*. 1989 Jul-Aug;**13**(4):421-5.
55. Shenkin A, Fraser WD, McLelland AJ, Fell GS, Garden OJ. Maintenance of vitamin and trace element status in intravenous nutrition using a complete nutritive mixture. *JPEN J Parenter Enteral Nutr*. 1987 May-Jun;**11**(3):238-42.
56. Lane HW, Lotspeich CA, Moore CE, Ballard J, Dudrick SJ, Warren DC. The effect of selenium supplementation on selenium status of patients receiving chronic total parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 1987 Mar-Apr;**11**(2):177-82.
57. Mansell P, Rawlings J, Allison S, et al. Reversal of a skeletal myopathy with selenium supplementation in a patient on home parenteral nutrition. *Clin Nutr*. 1987;**6**:179-83.
58. Shenkin A, Fell GS, Halls DJ, Dunbar PM, Holbrook IB, Irving MH. Essential trace

- element provision to patients receiving home intravenous nutrition in the United Kingdom. *Clin Nutr.* 1986 May;**5**(2):91-7.
59. Sriram K, O'Gara JA, Strunk JR, Peterson JK. Neutropenia due to copper deficiency in total parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 1986 Sep-Oct;**10**(5):530-2.
  60. Takagi Y, Okada A, Itakura T, Kawashima Y. Clinical studies on zinc metabolism during total parenteral nutrition as related to zinc deficiency. *JPEN J Parenter Enteral Nutr.* 1986 Mar-Apr;**10**(2):195-202.
  61. Jacobson S, Plantin LO, Carlmark B. Urinary excretion and blood concentrations of trace elements and electrolytes during total parenteral nutrition in Crohn's disease. *Dig Dis Sci.* 1984 Jul;**29**(7):606-13.
  62. Younoszai HD. Clinical zinc deficiency in total parenteral nutrition: Zinc supplementation. *JPEN J Parenter Enteral Nutr.* 1983 Jan-Feb;**7**(1):72-4.
  63. Main AN, Hall MJ, Russell RI, Fell GS, Mills PR, Shenkin A. Clinical experience of zinc supplementation during intravenous nutrition in Crohn's disease: Value of serum and urine zinc measurements. *Gut.* 1982 Nov;**23**(11):984-91.
  64. Moran DM, Russo J, Jr., Bell LV. Zinc deficiency dermatitis accompanying parenteral nutrition supplemented with trace elements. *Clin Pharm.* 1982 Mar-Apr;**1**(2):169-76.
  65. Phillips GD, Garnys VP. Parenteral administration of trace elements to critically ill patients. *Anaesth Intensive Care.* 1981 Aug;**9**(3):221-5.
  66. Lowry SF, Smith JC, Jr., Brennan MF. Zinc and copper replacement during total parenteral nutrition. *Am J Clin Nutr.* 1981 Sep;**34**(9):1853-60.
  67. Allen JI, Kay NE, McClain CJ. Severe zinc deficiency in humans: Association with a reversible T-lymphocyte dysfunction. *Ann Intern Med.* 1981 Aug;**95**(2):154-7.
  68. Lowry SF, Goodgame JT, Jr., Smith JC, et al. Abnormalities of zinc and copper during total parenteral nutrition. *Ann Surg.* 1979 Jan;**189**(1):120-8.
  69. Faintuch J, Faintuch JJ, Toledo M, Nazario G, Machado MC, Raia AA. Hyperamylasemia associated with zinc overdose during parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 1978 Nov;**2**(5):640-5.
  70. Strobel CT, Byrne WJ, Abramovits W, Newcomer VJ, Bleich R, Ament ME. A zinc-deficiency dermatitis in patients on total parenteral nutrition. *Int J Dermatol.* 1978 Sep;**17**(7):575-81.
  71. Messing B, Poitras P, Bernier IJ. Zinc deficiency in total parenteral nutrition. *Lancet.* 1977 Jul 9;**2**(8028):97-8.
  72. Brocks A, Reid H, Glazer G. Acute intravenous zinc poisoning. *Br Med J.* 1977 May

28;**1**(6073):1390-1.

73. Fleming CR, Hodges RE, Hurley LS. A prospective study of serum copper and zinc levels in patients receiving total parenteral nutrition. *Am J Clin Nutr.* 1976 Jan;**29**(1):70-7.
74. Kay RG, Tasman-Jones C, Pybus J, Whiting R, Black H. A syndrome of acute zinc deficiency during total parenteral alimentation in man. *Ann Surg.* 1976 Apr;**183**(4):331-40.
75. Tucker SB, Schroeter AL, Brown PW, Jr., McCall JT. Acquired zinc deficiency. Cutaneous manifestations typical of acrodermatitis enteropathica. *JAMA.* 1976 May 31;**235**(22):2399-402.
76. Weismann K, Hjorth N, Fischer A. Zinc depletion syndrome with acrodermatitis during longterm intravenous feeding. *Clin Exp Dermatol.* 1976 Sep;**1**(3):237-42.
77. Kay RG, Tasman-Jones C. Acute zinc deficiency in man during intravenous alimentation. *Aust N Z J Surg.* 1975 Nov;**45**(4):325-30.
78. Cvijanovich NZ, King JC, Flori HR, Gildengorin G, Vinks AA, Wong HR. Safety and dose escalation study of intravenous zinc supplementation in pediatric critical illness. *JPEN J Parenter Enteral Nutr.* 2016 Aug;**40**(6):860-8.
79. Davis C, Javid PJ, Horslen S. Selenium deficiency in pediatric patients with intestinal failure as a consequence of drug shortage. *JPEN J Parenter Enteral Nutr.* 2014 Jan;**38**(1):115-8.
80. Etani Y, Nishimoto Y, Kawamoto K, et al. Selenium deficiency in children and adolescents nourished by parenteral nutrition and/or selenium-deficient enteral formula. *J Trace Elem Med Biol.* 2014 Oct;**28**(4):409-13.
81. Ruktanonchai D, Lowe M, Norton SA, et al. Zinc deficiency-associated dermatitis in infants during a nationwide shortage of injectable zinc - Washington, DC, and Houston, Texas, 2012-2013. *MMWR Morb Mortal Wkly Rep.* 2014 Jan 17;**63**(2):35-7.
82. Barbarot S, Chantier E, Kuster A, et al. Symptomatic acquired zinc deficiency in at-risk premature infants: High dose preventive supplementation is necessary. *Pediatr Dermatol.* 2010 Jul-Aug;**27**(4):380-3.
83. 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 Jun;**19**(4):268-72.
84. Fok TF, Chui KK, Cheung R, Ng PC, Cheung KL, Hjelm M. Manganese intake and cholestatic jaundice in neonates receiving parenteral nutrition: A randomized controlled study. *Acta Paediatr.* 2001 Sep;**90**(9):1009-15.
85. Mouser JF, Hak EB, Helms RA, Christensen ML, Storm MC. Chromium and zinc concentrations in pediatric patients receiving long-term parenteral nutrition. *Am J Health*

Syst Pharm. 1999 Oct 1;**56**(19):1950-6.

86. Daniels L, Gibson R, Simmer K. Randomised clinical trial of parenteral selenium supplementation in preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 1996 May;**74**(3):F158-64.
87. Fell JM, Reynolds AP, Meadows N, et al. Manganese toxicity in children receiving long-term parenteral nutrition. *Lancet.* 1996 May 4;**347**(9010):1218-21.
88. 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 Jul-Aug;**19**(4):310-2.
89. Moukarzel AA, Song MK, Buchman AL, et al. Excessive chromium intake in children receiving total parenteral nutrition. *Lancet.* 1992 Feb 15;**339**(8790):385-8.
90. Suita S. Zinc in pediatric surgery. *J Nutr Sci Vitaminol (Tokyo).* 1992;**Spec No**:534-7.
91. Huston RK, Jelen BJ, Vidgoff J. Selenium supplementation in low-birthweight premature infants: Relationship to trace metals and antioxidant enzymes. *JPEN J Parenter Enteral Nutr.* 1991 Sep-Oct;**15**(5):556-9.
92. Newly recognized signs of selenium deficiency in humans. *Nutr Rev.* 1989;**47**(4):117-9.
93. Kelly DA, Coe AW, Shenkin A, Lake BD, Walker-Smith JA. Symptomatic selenium deficiency in a child on home parenteral nutrition. *J Pediatr Gastroenterol Nutr.* 1988 Sep-Oct;**7**(5):783-6.
94. Vinton NE, Dahlstrom KA, Strobel CT, Ament ME. Macrocytosis and pseudoalbinism: Manifestations of selenium deficiency. *J Pediatr.* 1987 Nov;**111**(5):711-7.
95. Dahlstrom KA, Ament ME, Medhin MG, Meurling S. Serum trace elements in children receiving long-term parenteral nutrition. *J Pediatr.* 1986 Oct;**109**(4):625-30.
96. Kien CL, Veillon C, Patterson KY, Farrell PM. Mild peripheral neuropathy but biochemical chromium sufficiency during 16 months of "chromium-free" total parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 1986 Nov-Dec;**10**(6):662-4.
97. Tokuda Y, Yokoyama S, Tsuji M, Sugita T, Tajima T, Mitomi T. Copper deficiency in an infant on prolonged total parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 1986 Mar-Apr;**10**(2):242-4.
98. Lockitch G, Pendray MR, Godolphin WJ, Quigley G. Serial changes in selected serum constituents in low birth weight infants on peripheral parenteral nutrition with different zinc and copper supplements. *Am J Clin Nutr.* 1985 Jul;**42**(1):24-30.
99. 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 May;**104**(5):763-8.

100. Suita S, Ikeda K, Hayashida Y, Naito K, Handa N, Doki T. Zinc and copper requirements during parenteral nutrition in the newborn. *J Pediatr Surg.* 1984 Apr;**19**(2):126-30.
101. Kien CL, Ganther HE. Manifestations of chronic selenium deficiency in a child receiving total parenteral nutrition. *Am J Clin Nutr.* 1983 Feb;**37**(2):319-28.
102. Rothbaum RJ, Maur PR, Farrell MK. Serum alkaline phosphatase and zinc undernutrition in infants with chronic diarrhea. *Am J Clin Nutr.* 1982 Mar;**35**(3):595-8.
103. Schwarz K, Peden VH, Craddock T. Zinc deficiency in a premature infant with severe short bowel syndrome. *Nutr Rev.* 1982 Mar;**40**(3):81-3.
104. Arlette JP, Johnston MM. Zinc deficiency dermatosis in premature infants receiving prolonged parenteral alimentation. *J Am Acad Dermatol.* 1981 Jul;**5**(1):37-42.
105. Vileisis RA, Deddish RB, Fitzsimons E, Hunt CE. Serial serum zinc levels in preterm infants during parenteral and enteral feedings. *Am J Clin Nutr.* 1981 Dec;**34**(12):2653-7.
106. Weber TR, Sears N, Davies B, Grosfeld JL. Clinical spectrum of zinc deficiency in pediatric patients receiving total parenteral nutrition (TPN). *J Pediatr Surg.* 1981 Jun;**16**(3):236-40.
107. Michie DD, Wirth FH. Plasma zinc levels in premature infants receiving parenteral nutrition. *J Pediatr.* 1978 May;**92**(5):798-800.
108. Suita S, Ikeda K, Nagasaki A, Hayashida Y. Zinc deficiency during total parenteral nutrition in childhood. *J Pediatr Surg.* 1978 Feb;**13**(1):5-9.
109. Lockitch G, Godolphin W, Pendray MR, Riddell D, Quigley G. Serum zinc, copper, retinol-binding protein, prealbumin, and ceruloplasmin concentrations in infants receiving intravenous zinc and copper supplementation. *J Pediatr.* 1983 Feb;**102**(2):304-8.
110. Aschner JL, Anderson A, Slaughter JC, et al. Neuroimaging identifies increased manganese deposition in infants receiving parenteral nutrition. *Am J Clin Nutr.* 2015 Dec;**102**(6):1482-9.
111. 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 Apr-Jun;**52**(2):94-9.
112. Jakubovic BD, Zipursky JS, Wong N, McCall M, Jakubovic HR, Chien V. Zinc deficiency presenting with necrolytic acral erythema and coma. *Am J Med.* 2015 Aug;**128**(8):e3-4.
113. 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 Oct 9;**2015**.
114. Vick G, Mahmoudizad R, Fiala K. Intravenous zinc therapy for acquired zinc deficiency

- secondary to gastric bypass surgery: A case report. *Dermatol Ther.* 2015 Jul-Aug;**28**(4):222-5.
115. Avila JD, Lacomis D. Proximal limb weakness in a patient with celiac disease: Copper deficiency, gluten sensitivity, or both as the underlying cause? *Case Rep Neurol Med.* 2016;**2016**:5415949.
116. 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**(1-2):173-7.
117. Dastych M, Jr., Senkyrik M, Dastych M, et al. Trace element status (zinc, copper, selenium, iron, manganese) in patients with long-term home parenteral nutrition. *Ann Nutr Metab.* 2016;**69**(2):120-4.
118. Greene E, Shokur R, Brown L, Petros A, Raman S. Incidence of hypermanganesemia in children who are administered parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2016 Aug;**40**(6):766-7.
119. Maskarinec SA, Fowler VG, Jr. Persistent rash in a patient receiving total parenteral nutrition. *Jama.* 2016 May 24-31;**315**(20):2223-4.
120. Moser O, Becker B, Hauch H, Woessmann W. Pancytopenia during parenteral nutrition. *Klin Padiatr.* 2016 Nov;**228**(6-07):332-3.
121. Rana J, Plovanich M, Wallace EB, Yang C, Canales AL, Mostaghimi A. Acquired acrodermatitis enteropathica after gastric bypass surgery responsive to IV supplementation. *Dermatol Online J.* 2016 Nov 15;**22**(11).
122. Salota R, Omar S, Sherwood RA, Raja K, Vincent RP. Clinical relevance of trace element measurement in patients on initiation of parenteral nutrition. *Ann Clin Biochem.* 2016 Nov;**53**(6):680-5.
123. Sant VR, Arnell TD, Seres DS. Zinc deficiency with dermatitis in a parenteral nutrition-dependent patient due to national shortage of trace minerals. *JPEN J Parenter Enteral Nutr.* 2016 May;**40**(4):592-5.
124. Walter E, Alsaffar S, Livingstone C, Ashley SL. Manganese toxicity in critical care: Case report, literature review and recommendations for practice. *J Intensive Care Soc.* 2016 Aug;**17**(3):252-7.
125. Zhu LY, Broussard KC, Boyd AS, Powers JG. An eruption while on total parenteral nutrition. *Cutis.* 2016 Mar;**97**(3):E3-5.
126. Cavallieri F, Fini N, Contardi S, Fiorini M, Corradini E, Valzania F. Subacute copper-deficiency myelopathy in a patient with occult celiac disease. *J Spinal Cord Med.* 2017 Jul;**40**(4):489-91.
127. Namjoshi SS, Muradian S, Bechtold H, et al. Nutrition deficiencies in children with

- intestinal failure receiving chronic parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2017 Feb 1;148607117690528.
128. Okhovat JP, O'Leary R, Hu M, Zussman J, Binder S, Worswick S. Acrodermatitis enteropathica in a patient with short bowel syndrome. *Cutis.* 2017 Nov;100(5):E4-E6.
  129. Oo TH, Hu S. Copper deficiency-related bone marrow changes secondary to long-term total parenteral nutrition. *Clin Case Rep.* 2017 Feb;5(2):195-6.
  130. Theilla M, Lawinski M, Cohen J, et al. Safety of home parenteral nutrition during pregnancy. *Clin Nutr.* 2017 Feb;36(1):288-92.
  131. Uzzan M, Kirchgesner J, Poupon J, Corcos O, Pinget I, Joly F. Antioxidant trace elements serum levels in long-term parenteral nutrition (PN): Prevalence and infectious risk associated with deficiencies, a retrospective study from a tertiary home-PN center. *Clin Nutr.* 2017 Jun;36(3):812-7.
  132. Van Gossum A, Pironi L, Chambrier C, et al. Home parenteral nutrition (HPN) in patients with post-bariatric surgery complications. *Clin Nutr.* 2017 Oct;36(5):1345-8.
  133. Wazir SM, Ghobrial I. Copper deficiency, a new triad: anemia, leucopenia, and myeloneuropathy. *J Community Hosp Intern Med Perspect.* 2017 Oct;7(4):265-8.
  134. Wu D, Fung MA, Kiuru M, Sharon VR. Acquired bullous acrodermatitis enteropathica as a histologic mimic of pemphigus foliaceus in a patient on parenteral nutrition. *Dermatol Online J.* 2017 Jul 15;23(7).
  135. Yanagisawa R, Takeuchi K, Komori K, et al. Hypoglycemia during the temporary interruption of parenteral nutrition infusion in pediatric hematopoietic stem cell transplantation. *JPEN J Parenter Enteral Nutr.* 2017 Nov;41(8):1414-8.
  136. Baruch D, Naga L, Driscoll M, Kao G. Acrodermatitis enteropathica from zinc-deficient total parenteral nutrition. *Cutis.* 2018 Jun;101(6):450-3.
  137. Capone K, Sriram S, Patton T, et al. Effects of chromium on glucose tolerance in infants receiving parenteral nutrition therapy. *Nutr Clin Pract.* 2018 Jun;33(3):426-32.
  138. Dressler A, Haiden N, Trimmel-Schwahofer P, et al. Ketogenic parenteral nutrition in 17 pediatric patients with epilepsy. *Epilepsia Open.* 2018 Mar;3(1):30-9.
  139. Gupta K, Wang H, Amin SB. Copper supplementation in premature infants with parenteral nutrition-associated cholestasis. *Nutr Clin Pract.* 2018 Oct;33(5):718-24.
  140. Jafari P, Thomas A, Haselbach D, et al. Trace element intakes should be revisited in burn nutrition protocols: A cohort study. *Clin Nutr.* 2018 Jun;37(3):958-64.
  141. Lin YT, Lan KM, Wang LK, Chen JY. Treatment of postherpetic neuralgia with intravenous administration of zinc sulfate: A case report. *A A Pract.* 2018 Jul 1;11(1):8-10.

142. Neelis E, Olieman J, Rizopoulos D, et al. Growth, body composition, and micronutrient abnormalities during and after weaning off home parenteral nutrition. *Journal of Pediatric Gastroenterology and Nutrition*. 2018 Nov;**67**(5):e95-e100.
143. Rehou S, Shahrokhi S, Natanson R, Stanojcic M, Jeschke MG. Antioxidant and trace element supplementation reduce the inflammatory response in critically ill burn patients. *J Burn Care Res*. 2018 Jan 1;**39**(1):1-9.
144. Franck AJ. Zinc deficiency in a parenteral nutrition-dependent patient during a parenteral trace element product shortage. *JPEN J Parenter Enteral Nutr*. 2014 Jul;**38**(5):637-9.
145. Chun JH, Baek JH, Chung NG, Kim JE, Cho BK, Park HJ. Development of bullous acrodermatitis enteropathica during the course of chemotherapy for acute lymphocytic leukemia. *Ann Dermatol*. 2011 Dec;**23**(Suppl 3):S326-8.
146. Shulman RJ. Zinc and copper balance studies in infants receiving total parenteral nutrition. *Am J Clin Nutr*. 1989 May;**49**(5):879-83.
147. Tulikoura I, Vuori E. Effect of total parenteral nutrition on the zinc, copper, and manganese status of patients with catabolic disease. *Scand J Gastroenterol*. 1986 May;**21**(4):421-7.
148. Jiang ZM, Yang NF, Jiao KS, Zhu Y, Fei LM, Tseng H. Postoperative fall in serum zinc concentrations unaffected by intravenous zinc therapy. *JPEN J Parenter Enteral Nutr*. 1985 Mar-Apr;**9**(2):196-8.
149. Serrano Ortega S, Aneiros Cachaza J, Tovar IV, Feijoo MF. Zinc deficiency dermatitis in parenteral nutrition: an electron-microscopic study. *Dermatologica*. 1985;**171**(3):163-9.
150. Zlotkin SH, Buchanan BE. Meeting zinc and copper intake requirements in the parenterally fed preterm and full-term infant. *J Pediatr*. 1983 Sep;**103**(3):441-6.
151. Brazin SA, Johnson WT, Abramson LJ. The acrodermatitis enteropathica-like syndrome. *Arch Dermatol*. 1979 May;**115**(5):597-9.
152. McCarthy DM, May RJ, Maher M, Brennan MF. Trace metal and essential fatty acid deficiency during total parenteral nutrition. *Am J Dig Dis*. 1978 Nov;**23**(11):1009-16.
153. Bos LP, van Vloten WA, Smit AF, Nube M. Zinc deficiency with skin lesions as seen in acrodermatitis enteropathica, and intoxication with zinc during parenteral nutrition. *Neth J Med*. 1977;**20**(6):263-6.
154. Arakawa T, Tamura T, Igarashi Y, Suzuki H, Sandstead HH. Zinc deficiency in two infants during total parenteral alimentation for diarrhea. *Am J Clin Nutr*. 1976 Feb;**29**(2):197-204.
155. Arakawa T, Tamura T, Igarashi Y, Suzuki H, Sandstead HH. Zinc deficiency in two infants during total parenteral nutrition for intractable diarrhea. *Acta Chir Scand Suppl*. 1976;**466**:16-7.

156. Hankins DA, Riella MC, Scribner BH, Babb AL. Whole blood trace element concentrations during total parenteral nutrition. *Surgery*. 1976 Jun;**79**(6):674-7.
157. Okada A, Takagi Y, Itakura T, Satani M, Manabe H. Skin lesions during intravenous hyperalimentation: zinc deficiency. *Surgery*. 1976 Nov;**80**(5):629-35.
158. Okada A, Takagi Y, Itakura T, Satani M, Manabe H. Zinc deficiency during intravenous hyperalimentation. *Acta Chir Scand Suppl*. 1976;**466**:18-9.
159. Solomons NW, Layden TJ, Rosenberg IH, Vo-Khactu K, Sandstead HH. Plasma trace metals during total parenteral alimentation. *Gastroenterology*. 1976 Jun;**70**(6):1022-5.
- CC: S Pinheiro / S Sandhu / W Hua / P Bright / M Iannacone / M Billings / S Jackson / A Chaudhry / P Calloway (DEPI)
- L Harinstein / J Klucken (DPV)
- B Nikhar / L Soule / J Meyer / A Rajpal / W-Y Gao / T Vu (DGIEP)

APPENDIX 1: Dietary Reference Intakes for zinc

**TABLE 1 Dietary Reference Intakes for Zinc by Life Stage Group**

Life stage group	DRI values (mg/day)				AI <sup>c</sup>	UL <sup>d</sup>
	EAR <sup>a</sup>		RDA <sup>b</sup>			
	males	females	males	females		
0 through 6 mo					2	4
7 through 12 mo	2.5	2.5	3	3		5
1 through 3 y	2.5	2.5	3	3		7
4 through 8 y	4.0	4.0	5	5		12
9 through 13 y	7.0	7.0	8	8		23
14 through 18 y	8.5	7.3	11	9		34
19 through 50 y	9.4	6.8	11	8		40
≥ 51 y	9.4	6.8	11	8		40
<b>Pregnancy</b>						
14 through 18 y		10.5		12		34
19 through 50 y		9.5		11		40
<b>Lactation</b>						
14 through 18 y		10.9		13		34
19 through 50 y		10.4		12		40

<sup>a</sup> **EAR** = Estimated Average Requirement.

<sup>b</sup> **RDA** = Recommended Dietary Allowance.

<sup>c</sup> **AI** = Adequate Intake.

<sup>d</sup> **UL** = Tolerable Upper Intake Level. Unless otherwise specified, the UL represents total intake from food, water, and supplements.

Source: Institute of Medicine. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Washington, DC: The National Academy Press; 2006.

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### APPENDIX 3: DEPI supplemental literature search

On January 21, 2019, DEPI used (b) (4) query language, reproduced below, to retrieve 260 PubMed records for articles published in 2015 or later.

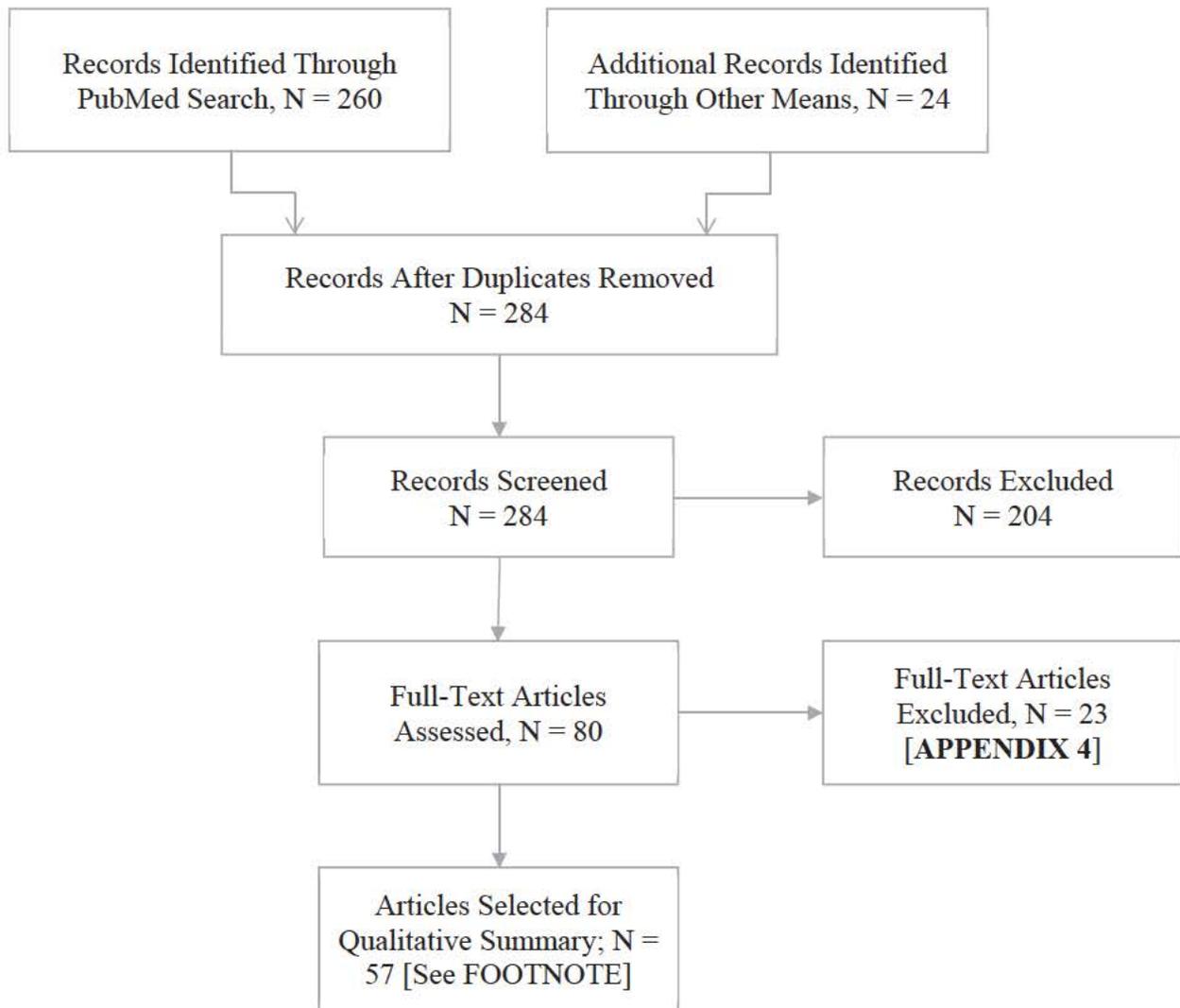


A DEPI analyst (JLW) hand searched the reference lists of recent or otherwise informative articles to identify and retrieve 21 additional PubMed records for evaluation.

On March 27, 2019, DEPI searched the Web of Science (WOS) Core Collection to identify 239 unique articles citing either one of two pivotal articles about zinc for parenteral nutrition [2, 7]. The DEPI analyst screened the titles for these 239 WOS records to identify and retrieve three final PubMed records for evaluation.

As summarized in Appendix Figure 1, a DEPI analyst (JLW) screened the titles and abstracts for the 284 unique PubMed records found by direct search or other means to select 80 articles for full-text examination. The full-text examination identified 57 full-text articles with results from original research (1) in patients given zinc parenterally or (2) about zinc status in patients on parenteral nutrition.

Appendix Figure 1: PRISMA flow diagram



FOOTNOTE: Includes four articles published in 2015 and captured by [10-12, 78].

(b) (4)

#### **APPENDIX 4: Full-text articles excluded from qualitative summary, by reason**

##### Reason excluded: Not original research (3 articles)

1. Fleming CR. Trace element metabolism in adult patients requiring total parenteral nutrition. *Am J Clin Nutr.* 1989 Mar;49(3):573-9.
2. Michie DD, MacFarlane MD, Wirth FH. Zinc and total parenteral nutrition. *South Med J.* 1977 Aug;70(8):985-7.
3. Plogsted S, Adams SC, Allen K, et al. Parenteral nutrition trace element product shortage Considerations. *Nutr Clin Pract.* 2016 Dec;31(6):843-7.

##### Reason excluded: Not human research (1 article)

4. Gagnon G, Voirol P, Soguel L, Boulat O, Berger MM. Trace element monitoring in the ICU: Quality and economic impact of a change in sampling practice. *Clin Nutr.* 2015 Jun;34(3):422-7.

##### Reason excluded: Limited relevance to trace elements and parenteral nutrition (3 articles)

5. Chandurkar V, Marliss EB. Multiple factors in recurrent symptomatic hypocalcemia following denosumab in a patient receiving home parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2016 Jul;40(5):734-8.
6. Jhangiani S, Prince L, Holmes R, Agarwal N. Clinical zinc deficiency during long-term total enteral nutrition. *J Am Geriatr Soc.* 1986 May;34(5):385-8.
7. Strathie Page S, Foster R. Acrodermatitis dysmetabolica in a child with cystic fibrosis. *Pediatr Dermatol.* 2016 Mar-Apr;33(2):e93-4.

##### Reason excluded: Not relevant to parenteral zinc or zinc status during parenteral nutrition (16 articles)

8. Chelkeba L, Ahmadi A, Abdollahi M, et al. The effect of parenteral selenium on outcomes of mechanically ventilated patients following sepsis: A prospective randomized clinical trial. *Ann Intensive Care.* 2015 Dec;5(1):29.
9. Chen CH, Harris MB, Partipilo ML, Welch KB, Teitelbaum DH, Blackmer AB. Impact of the nationwide intravenous selenium product shortage on the development of selenium deficiency in infants dependent on long-term parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2016 Aug;40(6):851-9.
10. Freitas R, Nogueira RJN, Cozzolino SMF, Vasques ACJ, Ferreira MT, Hessel G. [Is plasma selenium correlated to transthyretin levels in critically ill patients?]. *Nutr Hosp.* 2017 Jun 5;34(3):540-7.
11. Freitas R, Nogueira RJN, Cozzolino SMF, Vasques ACJ, Hessel G. Influence of selenium

supplementation on patients with inflammation: A pilot double blind randomized study. *Nutrition*. 2017 Sep;41:32-6.

12. Freitas R, Nogueira RJN, Hessel G. Selenium supplementation in pediatric patients using parenteral nutrition: Is it time to do something? *Rev Assoc Med Bras (1992)*. 2018 Mar;64(3):217-23.
13. Hantaweeant C, Chinthamittr Y, Siritanaratkul N. Anemia and neutropenia in copper-deficient patients: A report of two cases and literature review. *J Med Assoc Thai*. 2016 Jun;99(6):732-6.
14. 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 Jul;54(6):523-5.
15. 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 Jan;42(1):164-70.
16. Johnsen JC, Reese SA, Mackay M, Anderson CR, Jackson D, Paul IL. Assessing selenium, manganese, and iodine status in pediatric patients receiving parenteral nutrition. *Nutr Clin Pract*. 2017 Aug;32(4):552-6.
17. MacKay M, Mulroy CW, Street J, et al. Assessing copper status in pediatric patients receiving parenteral nutrition. *Nutr Clin Pract*. 2015 Feb;30(1):117-21.
18. Poujois A, Djebrani-Oussedik N, Ory-Magne F, Woimant F. Neurological presentations revealing acquired copper deficiency: Diagnosis features, aetiologies and evolution in seven patients. *Intern Med J*. 2018 May;48(5):535-40.
19. Schmidt T, Pargger H, Seeberger E, Eckhart F, von Felten S, Haberthur C. Effect of high-dose sodium selenite in cardiac surgery patients: A randomized controlled bi-center trial. *Clin Nutr*. 2018 Aug;37(4):1172-80.
20. Tramonti N, Lema J, Araujo MB, et al. Results of the implementation of a nutritional support protocol for major burn pediatric patients hospitalized in the intensive care unit. *Arch Argent Pediatr*. 2018 Aug 1;116(4):e515-e21.
21. Tumer Z, Petris M, Zhu S, et al. A 37-year-old Menkes disease patient—Residual ATP7A activity and early copper administration as key factors in beneficial treatment. *Clin Genet*. 2017 Nov;92(5):548-53.
22. van Rij AM, Thomson CD, McKenzie JM, Robinson MF. Selenium deficiency in total parenteral nutrition. *Am J Clin Nutr*. 1979 Oct;32(10):2076-85.

23. Yun JW, Woo YR, Kim M, Chung JH, Jung MH, Park HJ. Image Gallery: Leukonychia induced by selenium deficiency related to long-term parenteral nutrition in a patient with Hirschsprung disease. *Br J Dermatol.* 2017 Sep;177(3):e72.

## APPENDIX 5: DEPI quality check on safety reporting for NDA 209377

Organized by study design (as assessed by DEPI), the following tables show DEPI's quality check on the Luitpold presentation of safety results from clinical reports in medical literature. For abbreviations, see footnote after last table.

### Case reports, Part A

Author Year	Population	Location	Short Description
Brocks 1977 [72]	Adult	England	Crohn's disease patient inadvertently overdosed with zinc.
Weismann 1976 [76]	Adult	Denmark	Clinical zinc deficiency in two Crohn's disease patients on long-term PN.
Ruktanonchai 2014 [81]	Pediatric	U.S.	7 infants, including 4 low-birth-weight infants (<2500 gm), with clinical zinc deficiency on PN during U.S. TE shortage

### Case reports, Part B

Author Year	Dose	Safety Summary from Luitpold	DEPI Comment
Brocks 1977 [72]	3000 mg (as Zn sulfate) over 60 hours (1200 mg/24 hour for 2.5 days)	Fatal intoxication with acute hypotension, pulmonary edema, diarrhea, vomiting, jaundice, and oliguria.	High blood amylase also occurred.
Weismann 1976 [76]	135 mg/day oral (1 patient) and 12 mg/day IV (1 patient), both as Zn sulfate, with skin rash resolved within 2 weeks	No safety information reported.	Zinc administered "without any side effects."
Ruktanonchai 2014 [81]	Zn restored to PN in 6 infants, doses not reported	1 zinc-exposed infant died from conditions unrelated to zinc deficiency.	No comment.

### Descriptive studies, Part A

Author Year	Population	Location	N	Short Description
Btaiche 2011 [15]	Adult	U.S.	26	Patients receiving home PN for $\geq 1$ year between May 2002 and April 2007.
Ishizuka 2011 [16]	Adult	Japan	46	Patients treated with PN through a Department of Gastroenterological Surgery between October 2007 and August 2009.
Jacobson 1984 [61]	Adult	Sweden	6	Patients with Crohn's disease on long-term PN (mean 90 days, range 77-104 days).
Main 1982 [63]	Adult	Scotland	10	Patients with Crohn's disease.
Faintuch 1978 [69]	Adult	Brazil	7	PN patients with esophageal disease (N=4), intestinal fistula (N=2), or short bowel syndrome (N=1) inadvertently overdosed with zinc.

### Descriptive studies, Part B

Author Year	Parenteral Zinc Dose	Safety Summary from Luitpold	DEPI Comment
Btaiche 2011 [15]	mean 7.65 mg/day, range 3-15 mg/day, for mean 4.26 years	No safety information reported.	Clinical TE toxicities not observed; serum [Zn] >150 µg/dL in 6 of 146 (4%) samples.
Ishizuka 2011 [16]	6.5 mg/day with 25 of 46 (54%) on PN for >28 days	No safety information reported.	Clinical side effects from TEs not observed.
Jacobson 1984 [61]	1.2-2.0 mg/day over first 54-79 days of PN	No safety information reported.	No significant technical or metabolic complications. One patient with a minor liver disorder.
Main 1982 [63]	2.7-8.2 mg/day (as Addamel KabiVitrum and Zn sulfate) for mean 49.7 days, range 27-100 days	Major complications: superior vena cava obstruction (1 patient); other occurrences: severe diarrhea (4 patients), sepsis (1 patient), infection in intravenous line (several patients).	No comment.
Faintuch 1978 [69]	Estimated total 50-75 mg/day (~88% as added Zn sulfate) for mean 46 days, range 26-60 days	Blood amylase measured in 6 patients at 1.8-6.0 x upper limit of normal; 5 of 7 patients died from infection; serum [Zn] during overdose measured at mean 490 µg/dL, range 310-670 µg/dL.	No comment.

### Controlled studies, Part A

Author Year	Population	Location	N <sub>1</sub>	N <sub>0</sub>	Short Description
Liu 2015 [10]	Adult	Taiwan	76	45	Malnourished colorectal cancer patients provided PN before surgery.
Berger 2007 [17]	Adult	Switzerland	11	10	Burn patients in ICU.
Berger 2001 [23, 24]	Adult	Switzerland	11	21	Trauma patients in ICU.
Berger 1998 [33]	Adult	Switzerland	10	10	Patients admitted to a burn unit, between February 1992 and November 1995 and assigned to high- or low-zinc groups.
Braunschweig 1997 [37]	Adult	U.S.	21	23	Patients admitted to hospital for pancreatitis (N=38) or sepsis (N=6).
Faure 1991 [49]	Adult	France	15	15	Patients immediately after major vascular surgery.
Chen 1991 [50]	Adult	Taiwan	8	9	Patients with malignant (N=13) or non-malignant (N=4) conditions.

**Controlled studies, Part A (continued)**

Author Year	Population	Location	N <sub>1</sub>	N <sub>0</sub>	Short Description
Cvijanovich 2015 [78]	Pediatric	U.S.	18	6	Critically ill children (1 month to 10 years in age) admitted to ICU.
Fok 2001 [84]	Pediatric	Hong Kong	123	121	Infants admitted to neonatal unit and expected to require PN for >2 weeks.
Suita 1984 [100]	Pediatric	Japan	12	10	Post-surgical newborn infants (12 full-term, 10 premature)

**Controlled studies, Part B**

Author Year	Parenteral Zinc Dose	Safety Summary from Luitpold	DEPI Comment
Liu 2015 [10]	3.0 mg/day for mean 5.2 days	Group differences summarized for post-operative outcomes of organ failure, phlebitis, infection, and anastomotic leak.	Non-randomized study with hospital death in 3 (4%) and 4 (9%) patients exposed and not-exposed to parenteral zinc, respectively.
Berger 2007 [17]	37.5 mg/day (as Zn gluconate) for 14-21 days	No safety information reported.	No toxicity observed.
Berger 2001 [23, 24]	13 mg/day (as Zn gluconate) for 5 days	Three deaths in groups not treated with zinc.	Randomized study with (1) infection requiring antibiotics in 3 (27%) and 10 (48%) patients and (2) death in 0 (0%) and 3 (14%) patients exposed and not-exposed to parenteral zinc, respectively. No signs of toxicity or other adverse effects observed during TE administration.
Berger 1998 [33]	26.3 or 6.8 mg/day, from all sources, for up to 8 days	Group differences summarized for inflammatory markers, including IL-6, C-reactive protein, and white blood cell counts.	Randomized study with acute respiratory distress syndrome (ARDS) in 4 (40%) and 8 (80%) patients from high- and low-zinc groups, respectively.
Braunschweig 1997 [37]	30 mg/day for 3 days	Body temperature significantly higher in zinc group during 4-day study period (p=0.036).	No comment.

Author Year	Parenteral Zinc Dose	Safety Summary from Luitpold	DEPI Comment
Faure 1991 [49]	30 mg/day (as Zn gluconate) for 3 days	No safety information reported.	Randomized study with healing complications in 0 (0%) and 4 (27%) patients from zinc and placebo groups, respectively.
Chen 1991 [50]	0.68 mg added to each liter of PN solution for mean 43 days, range 28-89 days	No safety information reported.	Randomized study with death in 1 (12.5%) and 2 (22%) patients from zinc and control groups, respectively.
Cvijanovich 2015 [78]	0.25 (6 patients), 0.50 (6 patients), or 0.75 (6 patients) mg/day for up to 7 days	Infusion well-tolerated; no study-related adverse events; no deaths.	Non-randomized dose-finding study. 4 of 6 children in highest zinc group achieved plasma [Zn] >120 µg/dL without apparent toxicity.
Fok 2001 [84]	0.25 mg/kg/day (as Peditrace) for median 20 days (IQR 9-52 days) vs. 0.04 mg/kg/day (as Ped-El) for median 23 days (IQR 9-48 days)	Group differences summarized for total mortality (13.8% vs. 9.9%) and cause-specific mortality.	Randomized study primarily about possible cholestasis from co-intervention with parenteral manganese.
Suita 1984 [100]	Early zinc (0.04 mg/kg/day added after 1 week on PN; total PN duration, mean 117 days) vs. late zinc (0.04 mg/kg/day added after 4 weeks on PN; total PN duration, 73 days)	No clinical findings of toxicity reported in infants with elevated plasma [Zn] (>150 to 270 µg/dL).	Randomized study.

ABBREVIATIONS: ICU, intensive care unit; IQR, inter-quartile range; IV, intravenous (*i.e.*, parenteral); PN, parenteral nutrition; TE, trace element; Zn, zinc; [Zn], zinc concentration; N<sub>1</sub>, number of patients on parenteral zinc; N<sub>0</sub>, number of patients not on parenteral zinc, except where indicated by Parental Zinc Dose.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/  
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JOEL L WEISSFELD  
04/30/2019 01:58:43 PM

PATRICIA L BRIGHT  
04/30/2019 02:02:16 PM

SUKHMINDER K SANDHU  
04/30/2019 05:24:53 PM

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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 11, 2019

Requesting Office or Division: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Application Type and Number: NDA 209377

Product Name and Strength: Zinc Sulfate injection, USP  
3 mg\*/mL and 5 mg\*/mL

Total Product Strength: 30 mg\*/10 mL and 25 mg\*/5 mL

Applicant/Sponsor Name: American Regent, Inc

FDA Received Date: April 10, 2019

OSE RCM #: 2018-2243-1

DMEPA Safety Evaluator: Melina Fanari, R.Ph.

DMEPA Team Leader: Sarah K. Vee, Pharm.D.

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## 1 PURPOSE OF MEMORANDUM

The Division of Gastroenterology and Inborn Errors Products requested we review the revised container labels and carton labeling for Zinc Sulfate injection (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review<sup>a</sup>.

## 2 CONCLUSION

We find the revised container labels and carton labeling acceptable from a medication error perspective. We have no further recommendations at this time.

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<sup>a</sup> Fanari, Melina. Label and Labeling Review for Zinc Sulfate Injection (NDA 209377). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Mar 13. RCM No.: 2019-2243.

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/s/

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MELINA N FANARI  
04/11/2019 02:14:41 PM

SARAH K VEE  
04/11/2019 02:38:26 PM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**      Public Health Service

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**Division of Pediatric and Maternal Health Memorandum**

**Date:** March 29, 2019                      **Date Consulted:** October 29, 2018

**From:** Kristie Baisden, DO, Medical Officer, Maternal Health  
Division of Pediatric and Maternal Health (DPMH)

**Through:** Tamara Johnson, MD, MS, Team Leader, Maternal Health  
Division of Pediatric and Maternal Health (DPMH)

Lynne Yao, MD, Director  
Division of Pediatric and Maternal Health (DPMH)

**To:** Thao Vu, Regulatory Project Manager (RPM)  
Division of Gastroenterology and Inborn Error Products (DGIEP)

**Drug:** Zinc Sulfate Injection

**NDA:** 209377

**Proposed Indication:** A source of zinc for parental nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated

**Applicant:** American Regent, Inc.

**Subject:** Pregnancy and Lactation labeling

**Materials Reviewed:**

- NDA 209377 submitted on October 12, 2018
- Applicant's response to the information request (IR) for a review and summary of the relevant nonclinical and clinical data to support the proposed PLLR labeling submitted on November 29, 2018.
- DPMH Review of Selenious acid injection by Carrie Ceresa, Pharm D., MPH, dated February 4, 2019.

- DPMH Review of Travasol (amino acids) Injection by Jane Liedtka, MD, dated August 19, 2016.<sup>1</sup>

**Consult Question:** DGEIP requests review of PLLR labeling for this new NDA

## INTRODUCTION

On October 12, 2018, the applicant, Luitpold Pharmaceuticals, Inc., submitted an original new drug application (NDA) for Zinc Sulfate Injection via the 505(b)(2) regulatory pathway. The Division of Gastroenterology and Inborn Error Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) on October 29, 2018, to assist with the labeling review for the *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections.

## BACKGROUND

### Regulatory History

- Zinc Sulfate Injection is an essential trace element with the proposed indication as a source of zinc for parental nutrition when oral or enteral nutrition is not possible, sufficient, or contraindicated.
- Zinc Sulfate Injection has been available for over 30 years as an unapproved marketed product. The applicant is relying on the published literature for this 505(b)(2) application.
- On November 16, 2018, the Agency sent the applicant an Information Request (IR) for a review and summary of the relevant nonclinical and clinical data to support the proposed PLLR labeling.
- On November 29, 2018, the applicant submitted the requested information.

### Zinc Sulfate Injection Drug Characteristics<sup>2</sup>

- *Drug Class:* essential trace element
- *Mechanism of action (MOA):* the three broad biological functions and MOAs for zinc include catalytic, structural, and regulatory activities.
- *Dosage forms and strengths:* 3 mg zinc/mL (30mg/10mL) or 5 mg zinc/mL (25 mg/5 ml)
- *Dosage and administration:* (b) (4)
- *Adverse reactions:* (b) (4)

### Practice Guidelines for Parenteral Nutrition in Pregnancy<sup>3</sup>

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.

<sup>1</sup> DPMH did not rely on data in the Travasol NDA or the agency's finding of safety and effectiveness for Travasol to support labeling sections of this Zinc Sulfate Injection NDA. Rather, the cross-reference to the Travasol consult is included to avoid duplicating background information relevant to this class of parental nutrition products.

<sup>2</sup> Zinc Sulfate Injection (NDA 209377) proposed prescribing information

<sup>3</sup> ACOG Practice Bulletin Clinical Management Guidelines for Ob/Gyns, No. 189. Nausea and Vomiting of Pregnancy, January 2018.

### *Reviewer's Comment*

*DPMH previously reviewed the published literature related to the effects of malnutrition in pregnancy.<sup>4</sup> DPMH concluded severe malnutrition in pregnancy is associated with adverse maternal and fetal outcomes including preterm delivery, low birth weight, intrauterine growth restriction, congenital malformations, and perinatal mortality.*

*Maternal zinc deficiency is also associated with adverse pregnancy outcomes including fetal loss, congenital malformations, intrauterine growth restriction, low birth weight, prolonged labor, and preterm or post-term deliveries.<sup>5</sup> Therefore, DPMH recommends subsection 8.1 of labeling for Zinc Sulfate Injection include a Clinical Consideration informing prescribers of the risks of maternal zinc deficiency.*

## **REVIEW**

### ***PREGNANCY***

#### Nonclinical Experience

Animal reproduction studies have not been conducted with Zinc Sulfate Injection.

#### Applicant's Review of Pharmacovigilance Database

- The applicant searched the U.S. FDA Adverse Event Reporting System (FAERS) for cases of zinc sulfate use in pregnancy. A total of 2 cases were retrieved as below:
  - Case 10467076 reported exposure during pregnancy with events of gestational diabetes, pre-eclampsia, proteinuria, failed induction of labor, and portal hypertension. Concomitant meds: oxytocin, methyldopa
  - Case 10094340 reported exposure during pregnancy with no adverse event, normal newborn. Concomitant meds: srycel, hydroa, aspirin, and tylenol
- The applicant noted they have maintained a database of reportable adverse events since 2006. The applicant performed a cumulative search of their safety database from January 1, 2006 to November 16, 2018. The search encompassed the following: "Concentrated Zinc Sulfate Injection, USP (8105-25) and Zinc Sulfate Injection, USP (6110-25)." The search yielded spontaneous adverse events being reported for a total of 4 cases and none were related to pregnancy.

#### Applicant's Review of Published Literature

The applicant performed a literature search in PubMed, Embase, and Cochrane Reviews for articles relevant to zinc sulfate and pregnancy. The applicant submitted 2 articles as summarized below:

- A randomized double-blind placebo-controlled trial<sup>6</sup> involving the treatment of 284 pregnant women with below median plasma zinc levels at enrollment in prenatal care with 25 mg of oral zinc starting in the 2<sup>nd</sup> trimester. Infants in the zinc supplementation group had significantly greater birth weight (126 grams, p=0.03) and

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<sup>4</sup> DPMH Review of Travasol (amino acids) Injection by Jane Liedtka, MD, dated August 19, 2016.

<sup>5</sup> Chaffee B, et al. Effect of zinc supplementation on pregnancy and infant outcomes: a systematic review. Paediatr Perinat Epidemiol. 2012 Jul; 26 (01): 118-137.

<sup>6</sup> Goldenberg R, et al. The effect of zinc supplementation on pregnancy outcome. JAMA 1995; 274:463-468.

head circumference (0.4 cm, p=0.02). No adverse pregnancy outcomes related to oral zinc supplementation were reported.

- A Cochrane Database Systematic Review<sup>7</sup> which assessed the effects of oral zinc supplementation in pregnancy on maternal, fetal, neonatal, and infant outcomes. This review included 21 randomized controlled trials involving over 17,000 women and their babies. The daily oral dose of zinc ranged from 5 to 90 mg per day. The timing of zinc exposure in pregnancy varied between studies, with inclusion all of studies that initiated zinc prior to 27 weeks. Findings: zinc supplementation resulted in a small reduction in preterm birth (RR 0.86, 95% CI 0.76-0.97) in 16 RCTs of 7,637 women. No clear differences were seen between the zinc and no zinc groups for any other primary maternal or neonatal outcomes. The author's concluded the relative reduction in preterm birth was primarily represented by trials involving women of low income and could reflect general poor nutrition status. There was no convincing evidence that zinc supplementation in pregnancy results in other useful and important benefits.

#### DPMH's Review of Published Literature

This Reviewer performed a search in PubMed, Embase, Micromedex<sup>8</sup>, TERIS<sup>9</sup>, Reprotox<sup>10</sup>, and Briggs<sup>11</sup> to find relevant articles not cited by the applicant. Search terms included: "zinc sulfate" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," or "miscarriage."

- **Micromedex** states "safety for zinc sulfate use has not been established in pregnancy. Nutritional supplement doses of vitamin and minerals are generally considered safe during pregnancy. Dietary zinc requirements are increased during pregnancy to a recommended dietary reference intake of 11 mg daily, an amount 38% over non-reproducing adult women.<sup>12</sup> In animal reproductive studies, there was no fetal harm and no evidence of impaired fertility when pregnant rats, mice, rabbits and hamsters were given oral zinc sulfate doses up to 6 times the recommended human dose."<sup>13</sup>
- **Reprotox** states "Zinc is an essential nutrient. Although adverse pregnancy outcome has been associated with both high and low zinc tissue or blood concentrations, a role for excessive zinc intake in the production of congenital anomalies has not been established. The recommended daily allowance (RDA) for pregnant and lactating women is 11 and 12

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<sup>7</sup> Ota E, et al. Zinc supplementation for improving pregnancy and infant outcome. *Cochrane Database of Systematic Reviews 2015*, Issue 2. Art. No.:CD000230. DOI: 10.1002/14651858. CD000230.pub5.

<sup>8</sup>Truven Health Analytics information, <http://www.micromedexsolutions.com>, Accessed 2/13/19.

<sup>9</sup>TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 2/13/19.

<sup>10</sup>Reprotox® Website: [www.Reprotox.org](http://www.Reprotox.org). REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 2/13/19

<sup>11</sup> Briggs GG, et al. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*, 9<sup>th</sup> Ed. 2011.

<sup>12</sup> Picciano MF: Pregnancy and lactation: physiological adjustments, nutritional requirements and the role of dietary supplements. *J Nutr* 2003; 133:1997S-2002S.

<sup>13</sup> Product Information: GALZIN(R) oral capsules, zinc acetate oral capsules. Teva Pharmaceuticals USA Inc (per DailyMed), North Wales, PA, 2016.

mg, respectively.<sup>14</sup> The following studies are cited:

- A case-control study that reported finding serum zinc concentrations to be higher in a group of 69 pregnant women with prenatally confirmed fetal neural tube defects than in a group of 592 controls.<sup>15</sup> In contrast, decreases in serum zinc concentrations have also been reported in women carrying fetuses with neural tube defects.<sup>16,17,18,19,20</sup>
- A case-control study reported an estimated 2-fold increase in cleft lip/cleft palate risk with low maternal erythrocyte zinc.<sup>21</sup> In contrast, another case-control study did not find an association between maternal plasma zinc and cleft risk when they studied in a US population.<sup>22</sup>
- Multiple studies showing that the administration of oral zinc supplements to pregnant women did not significantly increase plasma zinc concentration<sup>23</sup> or improve pregnancy outcome.<sup>24,25,26,27,28,29</sup>
- Other studies reported increased body weight<sup>30</sup> and head circumference<sup>30,31</sup> in infants of orally zinc-supplemented pregnancies. In a cohort of 476 women, a low

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<sup>14</sup> Pitt JA, Zoellner MJ, Carney EW: Developmental toxicity of dietary zinc deficiency in New Zealand white rabbits. *Reprod Toxicol* 1997;11:781-9

<sup>15</sup> Mc Michael AJ, Dreosti IE, Ryan P et al: Neural tube defects and maternal serum zinc and copper concentrations in mid-pregnancy: a case-control study. *Med J Aust* 1994; 161:478-482.

<sup>16</sup> Cadver AO, Arcasoy A, Baycu T, Himmetoglu O. Zinc deficiency and anencephaly in Turkey. *Teratology* 1980;23:141.

<sup>17</sup> Gotalipoor MJ, Mansourian AR: Maternal zinc deficiency and neonatal neural tube defects in Gorgan-North of Iran. *Reprod Toxicol* 2005; 20(3):463-4.

<sup>18</sup> Cengiz B, Saylemez F, et al: Serum zinc, selenium, copper and lead levels in women with second-trimester induced abortion resulting from neural tube defects: a preliminary study. *Bio Trace Elem Res.* 2004; 97(3):225-35

<sup>19</sup> Carrillo-Ponce Mde L, Martanez-Ordaz, VA, et al: Serum lead, cadmium, and zinc levels in newborns with neural tube defects from a polluted zone in Mexico. *Reprod Toxicol.* 2004; 19(2):149-54.

<sup>20</sup> Dey AC, Shahidullah M, Mannan MA, Noor MK, Saha L, Rahman SA. Maternal and neonatal serum zinc level and its relationship with neural tube defects. *J Health Popul Nutr.* 2010 Aug;28(4):343-50.

<sup>21</sup> Krapels IP, Rooij IA, Wevers RA, et al: Myo-inositol, glucose and zinc status as risk factors for non-syndromic cleft lip with or without cleft palate in offspring: a case-control study. *BJOG.* 2004;111(7):661-8.

<sup>22</sup> Munger RG, Tamura T, Johnston KE, Feldkamp ML, Pfister R, Carey JC. Plasma zinc concentrations of mothers and the risk of oral clefts in their children in Utah. *Birth Defects Res A Clin Mol Teratol.* 2009 Feb;85(2):151-5.

<sup>23</sup> Hunt IF et al: Zinc supplementation during pregnancy: effects on selected blood constituents and on progress and outcome of pregnancy in low-income women of Mexican descent. *Am J Clin Nutr* 40:508-521, 1984.

<sup>24</sup> Campbell-Brown M et al: Zinc and copper in Asian pregnancies - is there evidence for a nutritional deficiency? *Br J Obstet Gynecol* 92:875-885, 1985

<sup>25</sup> Ghosh A et al: Zinc deficiency is not a cause for abortion, congenital abnormality and small-for-gestational age infant in Chinese women. *Br J Obstet Gynecol* 92: 886-91, 1985

<sup>26</sup> Mahomed K, James DK, Golding J, McCabe R: Zinc supplementation during pregnancy: a double blind randomized controlled trial. *Br Med J* 299:826-30, 1989

<sup>27</sup> Caulfield LE; Zavaleta N; Figueroa A; Leon Z: Maternal zinc supplementation does not affect size at birth or pregnancy duration in Peru. *J Nutr* 1999;129:1563-8.

<sup>28</sup> Hamadani JD, Fuchs GJ, Osendarp SJM et al: Zinc supplementation during pregnancy and effects on mental development and behaviour of infants: a follow-up study. *Lancet* 360:290-4, 2002

<sup>29</sup> Saaka M, Oosthuizen J, Beatty S. Effect of prenatal zinc supplementation on birthweight. *J Health Popul Nutr.* 2009 Oct;27(5):619-31.

<sup>30</sup> Goldenberg RL, Tsunenobu T, Neggers Y et al: The effect of zinc supplementation on pregnancy outcome. *JAMA* 274:463-8, 1995

<sup>31</sup> Danesh A, Janghorbani M, Mohammadi B. Effects of zinc supplementation during pregnancy on pregnancy outcome in women with history of preterm delivery: a double-blind randomized, placebo-controlled trial. *J Matern Fetal Neonatal Med.* 2010 May;23(5):403-8.

- concentration of serum zinc was related to the incidence of low birth weight.<sup>32</sup>
- A 2015 population-based birth cohort study from China observed that low maternal zinc concentrations during pregnancy were associated with a risk of fetal growth restriction and low birth weight<sup>33</sup> and inversely associated with a risk of preterm birth.<sup>34</sup>
  - In randomized double-blind controlled trial<sup>35</sup>, healthy pregnant women in Egypt at less than 16 weeks gestation with low serum zinc were administered oral zinc supplements (30 mg zinc sulfate) with or without additional multivitamins. Zinc supplements alone and combined with multivitamins reduced second- and third-stage complications during delivery. Rates for stillbirth and preterm delivery were lower among both zinc-supplemented groups compared to the placebo group. Early neonatal mortality was also significantly lower in the supplemented groups.

#### *Reviewer's Comment*

*Published data regarding zinc sulfate use during pregnancy is limited to oral supplementation. Overall, the reports do not provide a clear association of adverse pregnancy outcomes associated with zinc sulfate use in pregnant women. Furthermore, Zinc Sulfate Injection in parental nutrition has been marketed for over 30 years without any consistent reports of adverse pregnancy outcomes.*

## **LACTATION**

### Nonclinical Experience

Animal lactation studies have not been performed with Zinc Sulfate Injection.

### Applicant's Review of Pharmacovigilance Database

The applicant noted they have maintained a database of reportable adverse events since 2006. The applicant performed a cumulative search of their safety database from January 1, 2006 to November 16, 2018. The search encompassed the following: "Concentrated Zinc Sulfate Injection, USP (8105-25) and Zinc Sulfate Injection, USP (6110-25)." The search yielded spontaneous adverse events being reported for a total of 4 cases, none were related to breastfeeding or lactation.

### Applicant's Review of Published Literature

The applicant performed a literature search in PubMed, Embase, and Cochrane Reviews for articles relevant to zinc sulfate and lactation. No articles were submitted.

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<sup>32</sup> Neggars YH, Cutter GR, Acton RT et al: A positive association between maternal serum zinc concentration and birth weight. Am J Clin Nutr 51:678-84, 1990.

<sup>33</sup> Wang H, Hu Y-F, Hao J-H, Chen Y-H, Su P-Y, Wang Y, Yu Z, Fu L, Xu Y-Y, Zhang C, Tao F-B, Xu D-X. 2015. Maternal zinc deficiency during pregnancy elevates the risks of fetal growth restriction: a population-based birth cohort study. Nature Scientific Reports 5:11262. DOI: 1-.1-38/srep11262. <http://www.nature.com/scientificreports/>

<sup>34</sup> Wang H, Hu YF, Hao JH, Chen YH, Wang Y, Zhu P, Zhang C, Xu YY, Tao FB, Xu DX. 2016. Maternal serum zinc concentration during pregnancy is inversely associated with risk of preterm birth in a Chinese Population. J Nutr 146(3): 509-515

<sup>35</sup> Nossier SA, Naeim NE, El-Sayed NA, Abu Zeid AA. 2015. The effect of zinc supplementation on pregnancy outcomes: a double-blind, randomized controlled trial, Egypt. Br J Nutr doi:10.1017/S000711451500166X

## DPMH's Review of Published Literature

This Reviewer performed a search in *Medications and Mother's Milk*<sup>36</sup>, LactMed<sup>37</sup>, Micromedex<sup>8</sup>, Reprotox<sup>10</sup>, Briggs<sup>11</sup>, PubMed, and Embase using the terms “zinc sulfate” AND “lactation” OR “breastfeeding.”

- *Medications in Mother's Milk* lactation rating for zinc salts is “L2-limited data-probably compatible. One author has shown that zinc levels in breastmilk are independent of maternal plasma zinc concentrations or dietary zinc intake (see study details below).<sup>38</sup> Other body pools of zinc (i.e., liver and bone) are perhaps the source of zinc in breastmilk. Therefore, higher levels of oral zinc intake probably have minimal effect on zinc concentration in milk but excessive doses above the Recommended Daily Allowance (RDA) of 12-15 mg/day are not recommended.”
  - A randomized, double-blind trial<sup>38</sup> evaluated the effects oral zinc supplementation on maternal zinc status and milk zinc concentrations through 7 months of lactation. A total of 71 lactating women received either a daily 15-mg zinc supplement (ZS, n = 40) or placebo (NZS, n = 31) started by 2 wk postpartum. Overall mean zinc intakes were 13.0 +/- 3.4 mg/d for the NZS group and 25.7 +/- 3.9 mg/d (including supplement) for the ZS group. Plasma zinc concentrations of the ZS group were significantly higher than those of the NZS group (P = 0.05). Milk zinc concentrations declined significantly over the course of the study for all subjects but were not affected by zinc supplementation. The mean dietary zinc intake observed in the nonsupplemented group was adequate to maintain normal maternal zinc status and milk zinc concentrations through 7 months of lactation.
- **Reprotox** states “zinc is found in human milk and readily absorbed by the neonate.<sup>39,40,41,42</sup> Maternal oral zinc supplements did not significantly alter milk zinc concentrations<sup>43</sup> and could not be effectively used to treat a neonate with zinc deficiency.<sup>44</sup> In a lactation study from Thailand, breastfed infants at 4 to 6 months of age had an increased risk of zinc deficiency associated with underlying maternal zinc

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<sup>36</sup> Hale, Thomas (2017) *Medications and Mother's Milk*. Amarillo, Texas. Hale Publishing.

<sup>37</sup> <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. Accessed 2/13/19

<sup>38</sup> Krebs NF, et al. Zinc supplementation during lactation: effects on maternal status and milk zinc concentrations. *Am J Clin Nutr* 1995; 61(5):1030-1036.

<sup>39</sup> Solomons NW: Biological availability of zinc in humans. *Am J Clin Nutrition* 35:1048-75, 1982.

<sup>40</sup> Krebs NF, Hambidge KM: Zinc requirements and zinc intakes of breast-fed infants. *Am J Clin Nutrition* 43:288-92, 1986.

<sup>41</sup> Casey CE, Neville MC, Hambridge KM: Studies in human lactation: secretion of zinc, copper and manganese in human milk. *Am J Clin Nutr* 49:773-85, 1989.

<sup>42</sup> Krebs NF, Reidinger CJ, Miller LV, Hambidge KM: Zinc homeostasis in breast-fed infants. *Pediatr Res* 1996; 39: 661-5.

<sup>43</sup> Moser-Veillon PB, Reynolds RD: A longitudinal study of pyridoxine and zinc supplementation of lactating women. *Am J Clin Nutr* 52:135-41, 1990.

<sup>44</sup> Moore CME, Moran JR, Greene HL: Zinc supplementation in lactating women: evidence for mammary control of zinc secretion. *J Pediatr* 105:600-2, 1984.

deficiency and lower zinc concentrations in maternal milk.<sup>45</sup>”

- **Micromedex** states “infant risk cannot be ruled out. Zinc has been observed in human breast milk and zinc-induced copper deficiency may occur in the nursing infant.<sup>46</sup>”
- A supplementation trial in Italy,<sup>47</sup> in which 11 breastfeeding women eating a traditional Italian diet without vitamin and mineral supplements were compared to 11 breastfeeding women enrolled in a nutrification program and given an oral nutritional supplement (containing 20 mg zinc sulfate, 2 mg copper sulfate, and 116 mcg potassium iodide). Samples of 10 mL of milk were collected at 3, 30, and 90 days postpartum. Zinc milk concentrations declined significantly over the study period for all lactating subjects, without differences in the rate of decline between the women who started supplementation during lactation and those who did not. The authors concluded that healthy, well-nourished lactating Italian women whose diet is adequate, the levels of zinc in milk are not influenced by short-term supplementary intakes and milk levels of zinc are maintained over different levels of intake of zinc.

#### *Reviewer’s Comment*

*Zinc is naturally found in breastmilk. There are no available data on the effects of Zinc Sulfate Injection on the levels of zinc in breastmilk; however, published literature do not suggest oral zinc sulfate supplementation effects the levels of zinc in breastmilk. This reviewer did not find any published literature reporting zinc-induced copper deficiency in a breastfed infant following maternal supplementation with zinc sulfate. Zinc-induced copper deficiency has been reported in association with excessive intake of zinc in adults and children.<sup>48</sup>*

### **FEMALES AND MALES OF REPRODUCTIVE POTENTIAL**

#### **Nonclinical Experience**

Animal studies have not been conducted with Zinc Sulfate Injection to establish the effects on fertility and reproductive performance.

#### **Applicant’s Review of Pharmacovigilance Database**

The applicant noted they have maintained a database of reportable adverse events since 2006. The applicant performed a cumulative search of their safety database from January 1, 2006 to November 16, 2018. The search encompassed the following: “Concentrated Zinc Sulfate Injection, USP (8105-25) and Zinc Sulfate Injection, USP (6110-25).” The search yielded spontaneous adverse events being reported for a total of 4 cases, none were related to fertility.

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<sup>45</sup> Dumrongwongsiri O, Suthutvoravut U, Chatvutinin S, Phoonlabdacha P, Sangcakul A, Siripinyanond A, Thiengmanee U, Chongviriyaphan N. 2015. Maternal zinc status is associated with breast milk zinc concentration and zinc status in breastfed infants aged 4-6 months. *Asia Pac J Clin Nutr* 24(2): 273-280

<sup>46</sup> Product Information: GALZIN(R) oral capsules, zinc acetate oral capsules. Teva Pharmaceuticals USA Inc (per DailyMed), North Wales, PA, 2016.

<sup>47</sup> Chierici R, et al. Dietary supplements for the lactating mother: influence on the trace element content of milk. *Acta Paediatr Suppl.* 1999 Aug; 88(430):7-13.

<sup>48</sup> Ozden T, et al. Copper, zinc, and iron levels in infants and their mothers during the first year of life: a prospective study. *BMC Pediatr.* 2015; 15:157.

### Applicant’s Review of Published Literature

The applicant performed a literature search in PubMed, Embase, and Cochrane Reviews for articles relevant to zinc sulfate and fertility. No relevant articles were identified.

### DPMH’s Review of Published Literature

This Reviewer performed a search in PubMed, Embase, and Reprotox<sup>10</sup> using the terms “zinc sulfate” AND “fertility,” “contraception,” “oral contraceptives,” OR “infertility.”

- **Reprotox** states “the role of zinc in male fertility is not clear. Some infertile men have low zinc concentrations in seminal fluid.<sup>49</sup> Correction of these levels with oral zinc therapy was found to have no effect<sup>50</sup> and to improve<sup>51,52</sup> sperm end points and fertility.”

## **DISCUSSION and CONCLUSIONS**

### Pregnancy

Zinc is an essential trace element needed to prevent zinc deficiency. Although animal reproduction studies have not been conducted with Zinc Sulfate Injection, the product has been used in humans for decades. Zinc Sulfate Injection is primarily used as a source of zinc in parental nutrition. Zinc Sulfate Injection is not expected to be harmful during pregnancy as there are no consistent reports of adverse pregnancy outcomes due to zinc supplementation in parental nutrition in pregnant women.

DPMH recommends subsection 8.1 of labeling state administration of the approved recommended dose of Zinc Sulfate Injection in parental nutrition is not expected to cause major birth defects, miscarriage, or adverse maternal or fetal outcomes. In addition, DPMH recommends adding a Clinical Considerations to inform prescribers of the risks associated with zinc deficiency in pregnancy along with recommendations to consider parental nutrition with zinc if a pregnant woman’s nutritional requirements cannot be fulfilled by oral or enteral intake.

### Lactation

DPMH recommends subsection 8.2 of labeling state that zinc is present in human milk. No adverse events have been reported in breastfed infants after maternal administration of oral zinc sulfate. Administration of the approved recommended dose of Zinc Sulfate Injection in parental nutrition is not expected to cause harm to a breastfed infant. There is no information on the effects of zinc sulfate on milk production. DPMH recommends including the following risk/benefit statement, “the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Zinc Sulfate Injection and any potential adverse effects on the breastfed infant from Zinc Sulfate Injection or from the underlying maternal condition.”

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<sup>49</sup> Sun J, Yu G, Zhang Y, Liu X, Du C, Wang L, Li Z, Wang C. 2016. Heavy metal level in human semen with different fertility: a meta-analysis. *Biol Trace Elem Res* DOI: 10.1007/s12011-016-0804-2

<sup>50</sup> Takihara H et al: Zinc sulfate therapy for infertile male with or without varicocele. *Urology* 29:638-41, 1987

<sup>51</sup> Tikkiwal M et al: Effect of zinc administration on seminal zinc and fertility of oligospermic males. *Ind J Physiol Pharmacol* 31:30-4, 1987.

<sup>52</sup> Omu AE, AL-Axemi MK, Kehinde EO et al: Indications of the mechanisms involved in improved sperm parameters by zinc therapy. *Med Princ Pract.*2008; 17(2):108-16

### Females and Males of Reproduction Potential

DPMH recommends subsection 8.3 of labeling be omitted. Limited available human data suggest zinc sulfate does not adversely affect fertility. Pregnancy testing and contraception subheadings are not recommended because there are no data to suggest zinc sulfate is associated with embryo-fetal toxicity.

### **LABELING RECOMMENDATIONS**

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR. The recommendations below are pending input from the Nonclinical Review Team. DPMH discussed our labeling recommendations with the Division at the March 13, 2019 labeling meeting. DPMH refers to the final NDA action for final labeling.

### **DPMH Proposed Zinc Sulfate Injection Pregnancy and Lactation Labeling**

### **FULL PRESCRIBING INFORMATION**

#### **8 USE IN SPECIFIC POPULATIONS**

##### **8.1 Pregnancy**

##### Risk Summary

Administration of the approved recommended dose of Zinc Sulfate Injection in parental nutrition is not expected to cause major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with Zinc Sulfate Injection.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In 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, is associated with adverse pregnancy and fetal outcomes. Pregnant women have an increased metabolic demand for trace elements, including zinc. Parental nutrition with zinc should be considered if a pregnant woman's nutritional requirements cannot be fulfilled by oral or enteral intake.

##### **8.2 Lactation**

##### Risk Summary

Zinc is present in human milk. Administration of the approved recommended dose of Zinc Sulfate Injection in parental nutrition is not expected to cause harm to a breastfed infant. There is no information on the effects of zinc sulfate on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Zinc Sulfate Injection and any potential adverse effects on the breastfed infant from Zinc Sulfate Injection or from the underlying maternal condition.

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04/02/2019 02:13:10 PM

LYNNE P YAO  
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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\*\*\***

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**Date of This Review:** March 13, 2019

**Requesting Office or Division:** Division of Gastroenterology and Inborn Errors Products (DGIEP)

**Application Type and Number:** NDA 209377

**Product Name and Strength:** Zinc Sulfate injection, USP  
3 mg\*/mL and 5 mg\*/mL

**Total Product Strength:** 30 mg\*/10 mL and 25 mg\*/5 mL

**Product Type:** Single Ingredient Product

**Rx or OTC:** Prescription (Rx)

**Applicant/Sponsor Name:** American Regent, Inc.

**FDA Received Dates:** October 12, 2018  
February 26, 2019  
March 8, 2019

**OSE RCM#:** 2018-2243

**DMEPA Safety Evaluator:** Melina Fanari, R.Ph.

**DMEPA Team Leader:** Sarah K. Vee, Pharm.D.

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## 1 REASON FOR REVIEW

As part of the approval process for Zinc Sulfate injection, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the proposed Zinc Sulfate injection prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS 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	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	B

N/A=not applicable for this review

\*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 FINDINGS AND RECOMMENDATIONS

During the mid-cycle meeting for this Application, the Office of Pharmaceutical Quality (OPQ) stated the product name and strength would follow the USP monograph. As recommended, the following format should be displayed on the container labels and carton labeling:

Zinc Sulfate Injection, USP 25 mg*/5 mL (5 mg*/mL) of Zinc
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Side panel:

\*Each mL provides 5 mg of zinc (present as (b) (4) mg of zinc sulfate)

Zinc Sulfate Injection, USP  
 30 mg\*/10 mL  
 (3 mg\*/mL) of Zinc

Side panel:

\*Each mL provides 3 mg of zinc (present as 7.41 mg of zinc sulfate)

Section 3 Dosage Forms and Strengths of the Prescribing Information should be revised to reflect this information. We defer to OPQ to provide revisions to this section.

Tables 2 below includes the identified medication error issues with the submitted container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for American Regent, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
<b>Container Label(s) and Carton Labeling</b>			
1.	The strength presentation is not consistent.	Inconsistent expression of strength can lead to confusion among healthcare providers.	<p>Revise the strength presentation for both strengths as follows:</p> <p><b>25 mg*/5 mL</b>            (5 mg*/mL)            of zinc</p> <p>Side panel:            *Each mL provides 5 mg of zinc            (present as (b) (4) mg of zinc sulfate)</p> <p><b>30 mg*/10 mL</b>            (3 mg*/mL)            of zinc</p> <p>Side panel:            *Each mL provides 3 mg of zinc            (present as 7.41 mg of zinc sulfate)</p>

**Table 2. Identified Issues and Recommendations for American Regent, Inc. (entire table to be conveyed to Applicant)**

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	There is inadequate differentiation between the 3 mg/mL and 5 mg/mL strengths.	Clearly differentiating the available strengths will minimize confusion and risk for wrong strength medication errors.	Revise all container labels and carton labeling to utilize a unique color for the 3 mg/mL and 5 mg/mL strengths and ensure that the color doesn't overlap between both strengths.
3.	The format for expiration date is not defined.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date 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.
4.	The net quantity statement is more prominent than the product strength statement and is located in close proximity to the product strength statement.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is more prominent and located in close proximity to the strength statement.	Decrease the prominence and relocate the net quantity statement away from the product strength, such as to the bottom of the principle display panel.

Table 2. Identified Issues and Recommendations for American Regent, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
5.	The dilution and admixing statement is absent.	We recommend adding a statement to inform healthcare providers that this product must be diluted and used as an admixture in parenteral nutrition solutions to minimize the risk of administering the drug as an intravenous bolus.	Revise the route of administration statement 'For intravenous use' to read:  'For intravenous use after dilution and admixing'.
6.	Negative statement (b) (4) identified.	Due to our understanding of post-marketing reports, negative statements may have the opposite of intended meaning because the word 'not' can be overlooked and the warning be misinterpreted as an affirmative action. <sup>a</sup>	Remove the negative statement (b) (4).
7.	The usual dose statement refers to PI as (b) (4).	As per 21 CFR 201.55, the usual dose statement is required on carton labels and container labeling.	Revise the statement; (b) (4) to read:  'Recommended Dose: See Prescribing Information'
<b>Carton Labeling</b>			
1.	The product identifier required under the drug supply chain security act (DSCSA) is missing.	DSCSA requires manufacturers and repackages, respectively, to affix or imprint a product identifier to each package and homogeneous case of a product intended to be introduced in a transaction in (to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

<sup>a</sup> Institute for Safe medication practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

#### **4 CONCLUSION**

We defer to OPQ to provide revisions to Section 3 Dosage Forms and Strengths in the prescribing information as discussed in Section 3. We have no additional recommendations for the PI as this time.

Our evaluation of the proposed Zinc Sulfate injection container label and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Applicant. We ask that the Division convey Table 2 in its entirety to American Regent, Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 4 presents relevant product information for Zinc Sulfate injection that American Regent, Inc. submitted on October 12, 2018, February 26, 2019 and March 8, 2019.

<b>Table 2. Relevant Product Information for Zinc Sulfate injection</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	Zinc sulfate
<b>Indication</b>	source of zinc for parental nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated
<b>Route of Administration</b>	Intravenous
<b>Dosage Form</b>	injection
<b>Strength</b>	30 mg*/10 mL (3 mg*/mL) and 25 mg*/5 mL (5 mg*/mL) of zinc
<b>Dose and Frequency</b>	<p>(b) (4)</p> <p>(b) (4)</p> <p>For the metabolically stable adult receiving parenteral nutrition, the suggested intravenous dosage is 3 mg/day.</p> <p>(b) (4)</p>
<b>How Supplied</b>	(b) (4)
<b>Storage</b>	Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]

## APPENDIX F. LABELS AND LABELING

### F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>b</sup> along with postmarket medication error data, we reviewed the following Zinc Sulfate injection labels and labeling submitted by American Regent, Inc.

- Container label(s) received on February 26, 2019 and March 8, 2019
- Carton labeling received on February 26, 2019 and March 8, 2019
- Prescribing Information (Image not shown) received on October 12, 2019



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<sup>b</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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