NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	NDA 209377
Priority or Standard	Standard
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Division/Office	Division of Gastroenterology and Inborn Errors Products /ODEIII
Review Completion Date	July 18, 2019
Established/Proper Name	Zinc Sulfate
(Proposed) Trade Name	None
Pharmacologic Class	Trace Element
Applicant	American Regent, Inc.
Dosage form	Injection
Applicant proposed Dosing Regimen	Weight/age: Dosage 10 kg and greater: 50 mcg/kg/day >5 kg to <10 kg: (b) (4) 100 mcg/kg/day >3 kg and <5 kg: 250 mcg/kg/day Preterm infant <3 kg: 400 mcg/kg/day Adults: 3 mg/day
Applicant Proposed Indication(s)/Population(s)	a source of zinc for parental nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	a source of zinc for parental nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.
Recommended Dosing Regimen	The dosage of Zinc Sulfate Injection should be individualized based on the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral zinc intake. Adults 3 mg/day for metabolically stable patients, with potential need for a higher daily dosage in monitored patients with small bowel fluid lost and excess stool or ileostomy output Pediatric Patients The dosages in the table below are general recommendations intended for most pediatric patients. However, based on clinical requirements, some patients may require a higher dosage.

Recommended Dosage of Zinc Sulfate Injection for Pediatric Patients by Age and Estimated Weight

Population	Estimated Weight for Age	Recommended Daily Dosage
Pediatric Patients	10 kg and above	50 mcg/kg (up to 3 mg/day)
	5 kg to less than 10 kg	100 mcg/kg
Term neonates	3 kg to less than 5 kg	250 mcg/kg*
Preterm neonate	Less than 3 kg	400 mcg/kg

*Term neonates have higher requirements in the first 3 months of life

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OPQ=Office of Pharmaceutical Quality
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DMEPA=Division of Medication Error Prevention and Analysis
DPV=Division of Pharmacovigilance
DRISK=Division of Risk Management
OPT=Office of Pediatric Therapeutics
OULDC=Office of Unapproved Drug Compliance
DPMH=Division of Pediatric and Maternal Health

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ASPEN	American Society for Parenteral and Enteral Nutrition
BLA	biologics license application
CAERS	Center for Food Safety and Applied Nutrition Adverse Event Reporting System
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
DEPI	Division of Epidemiology
DGIEP	Division of Gastroenterology and Inborn Errors Products
DPMH	Division of Pediatric and Maternal Health
DPV-I	Division of Pharmacovigilance I
EAR	estimated average requirement
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IND	investigational new drug
IOM	Institute of Medicine
IV	intravenous
MTE	multitrace
NDA	new drug application
(b) (4)	(b) (4)
NOAEL	no observable adverse effect level
PDE	permitted daily exposure
PK	pharmacokinetics
PN	parenteral nutrition
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
RDA	recommended dietary allowance
RDI	recommended daily intake
SLR	systematic literature review
TE	trace element
UL	tolerable upper intake level

1 Executive Summary

1.1.Product Introduction

The product under review is Zinc Sulfate Injection. Zinc is an essential trace element (TE) necessary in the diet to maintain health.

Zinc Sulfate Injection provides 30 mg/10 mL (3 mg/mL) and 25 mg/5 mL (5 mg/mL) of elemental zinc. The product will be supplied as a Pharmacy Bulk Package (10 mL vial or 5 mL vial) intended for admixture with parenteral nutrition (PN) and not for direct intravenous (IV) administration. The Applicant, American Regent (formerly known as Luitpold Pharmaceuticals), is not proposing a proprietary name. The Established Pharmacologic Class will be "trace element."

The Applicant's proposed indication for Zinc Sulfate Injection is a "source of zinc for parental nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated." The Applicant's proposed indication is for adult and pediatric patients.

The Food and Drug Administration (FDA) has previously approved the following products containing zinc: (i) Zinc chloride injection 1 mg/mL by Hospira Inc. (NDA 18959; currently available); (ii) Zinc Sulfate Injection 1 mg/mL by Abraxis Pharm. (NDA 19229; withdrawn on 10/11/16). However, the Applicant currently markets "Concentrated Zinc Sulfate Injection" (contains 5 mg/mL of elemental zinc) as an unapproved product and it has been used for close to 30 years "as a supplement to intravenous solutions given for TPN. Administration helps to maintain plasma levels and to prevent depletion of endogenous stores."[1] Zinc sulfate is also marketed, unapproved, by the Applicant in a fixed-combination trace element product (Multi-Trace 5: chromic chloride, cupric sulfate, manganese sulfate, selenious acid, and zinc sulfate heptahydrate).

Oral zinc is marketed as a dietary supplement.

The Applicant has proposed a dosing regimen of 3 mg/day for metabolically stable adult patients receiving PN (b) (4) he Applicant has also proposed a dosing regimen of 50 mcg/kg/day for patients 10 kg and greater, (b) (4) 100 mcg/kg/day for patients >5 kg to <10 kg, 250 mcg/kg/day for patients >3 kg and <5 kg, and 400 mcg/kg/day for preterm infants <3 kg.

[1] American Regent Inc. Concentrated Zinc Sulfate Injection, USP . Disclaimer: This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA. 2018 [Available from: https://dailymed.nlm.nih.gov/dailymed/druglnfo.cfm?setid=1a03fe85-fdc9-4847-960f-1fc782d7d493.]

The final agreed-upon dosing regimen in adults and pediatric patients can be found on the first page of this review.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted a literature-based 505(b)(2) application that includes clinical trials of intravenous zinc sulfate as supplement in PN solutions. No clinical trials of the proposed product, Zinc Sulfate Injection, have been conducted by the Applicant.

Zinc is an essential trace element. Zinc functions as a cofactor of various enzymes including DNA polymerases, RNA polymerases, alcohol dehydrogenase, and alkaline phosphatases. Zinc is a coordinator of protein structural folding, such as folding of "Zinc finger" motif that interacts with a variety of proteins, lipids, and nucleic acids. In addition, zinc is a catalyst of essential biochemical reactions, including activation of substrates of carbonic anhydrase in erythrocyte. Also, zinc is a signaling mediator modulating multiple signaling pathways.

Clinical manifestations of severe zinc deficiency include bullous pustular dermatitis, alopecia, diarrhea, emotional disorder, weight loss, intercurrent infections, hypogonadism in males; it is fatal if unrecognized and untreated. Manifestations of mild zinc deficiency include alopecia, diarrhea, growth retardation, delayed sexual maturation and impotence, eye and skin lesions, and impaired appetite. PN-dependent patients have developed a syndrome comparable to acrodermatitis enteropathica in the absence of adequate zinc supplementation.

Efficacy data from published clinical trials of intravenous zinc sulfate in the PN setting; nutritional requirements of oral/enteral zinc (i.e., Recommended Dietary Allowance or Reference Daily Intake (RDA, RDI) values); PN guidelines based on expert consensus, time and extent of use in clinical practice; and generally accepted scientific knowledge of zinc as an essential trace element, support a finding of substantial evidence of effectiveness of Zinc Sulfate Injection for the proposed indication in adult and pediatric patients as a "source of zinc for parental nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated."

1.3.Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Zinc is an essential trace element naturally present in many foods and is a constituent of various enzymes responsible for DNA replication, RNA transcription, and protein synthesis. It is currently marketed as an oral dietary supplement with an oral Reference Daily Intake (RDI) value of 11 mg/day for adults per 21 CFR 101.9. The proposed product, Zinc Sulfate Injection provides 30 mg/10 mL (3 mg/mL) zinc or 25 mg/5 mL (5 mg/mL) zinc and is recommended for approval as a source of zinc for parenteral nutrution (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated.

Parenteral nutrition without supplementation of zinc is likely to result in clinical deficiency. Zinc deficiency is the basis for the essential nature of zinc as a dietary nutrient for humans (1).

A variety of clinical presentations have been observed with zinc deficiency, largely owing to the wide range of biochemical and physiologic functions that require zinc. Clinical presentations, notable in many case reports of severe zinc deficiency during PN, include bullous-pustular dermatitis, alopecia, diarrhea, emotional disorder, weight loss, intercurrent infections, hypogonadism in males. Also, manifestations of mild zinc deficiency including alopecia, diarrhea, growth retardation, delayed sexual maturation and impotence, eye and skin lesions, and impaired appetite have been reported. Finally, PN-dependent patients have developed a syndrome comparable to acrodermatitis enteropathica in the absence of adequate zinc supplementation.

As the sole parenteral source, zinc sulfate products marketed unapproved since 1990 with the same active ingredient as the proposed product are oftentimes vulnerable to drug shortage and have frequently been on the drug shortage list since 2012. Drug shortages of parenteral zinc have been associated with clinical cases of zinc deficiency in premature infants (2). Approval of Zinc Sulfate Injection will provide a product that meets CMC quality standards.

Review of the efficacy and safety of Zinc Sulfate Injection has been based on data from a systematic literature review (SLR) commissioned by the Applicant and conducted by the (b) (4) identified 69 publications reporting on zinc exposure in adults and 31 in pediatric populations, including randomized, placebo- and active-controlled clinical trials in a range of patient populations (neonatal, pediatric, and adult), that primarily evaluate the effect of intravenous (IV) zinc supplementation in patients on chronic PN. An additional 34 publications not captured by (b) (4) based on an independent assessment of the SLR was identified during the NDA review. The

published studies include metabolic balance studies and controlled clinical studies with limited efficacy and safety assessments. The time and extent of parenteral zinc use in adults and pediatrics in clinical practice for PN supplementation purposes also supports the proposed use.

Adults

A study of the effects of doses of between 0 and 12 mg/day of parenteral zinc in adults for 3 weeks (3) found a positive correlation between the amount of zinc lost from the GI tract and the weight of the GI contents lost or excreted. In patients who did not lose >300 g/day of stool and/or small intestinal drainage, zinc balance was achieved with 3 mg/day of supplemental zinc. In patients with small bowel fluid loss and ileostomy, the amount of additional zinc needed to offset the fluid losses was determined based on a regression analysis. A study of patients 10 to 69 years of age receiving TE supplementation including zinc 2 mg/L vs. a control group not receiving TE supplementation (4) concluded that zinc 70 to 80 mcg/kg/day was appropriate in this population.

Pediatrics

- A study in eight infants and two children 2 and 8 years of age that studied the effect of zinc 30 or 50 mcg/kg/day in PN for approximately 4 weeks (5) concluded that higher doses (100 mcg/kg/day) are needed in this population.
- A study of infants/children 4 to 65 months of age given zinc 2 mg/L in PN for a mean duration of approximately 2 years (6) concluded that 70 to 80 mcg/kg/day was appropriate in this population.
- A study that randomized premature, full term SGA, and full term infants to 6 days of 140 mcg/kg/day, 290 mcg/kg/day, and 490 mcg/kg/day (7) concluded that 438 mcg/kg/day is required in pre-term infants, whereas, in full-term small for gestational age and full-term infants a dosage of above 150 mcg/kg/day is adequate.
- A study that randomized premature and full term infants to TPN supplemented with zinc 40 mcg/kg/day for 4 weeks after either 1 week on TPN or 4 weeks on TPN (8) concluded that 40 mcg/kg/day is sufficient in full term infants but not in premature infants or infants losing intestinal fluids.
- A metabolic balance study in premature infants weighing less than 1050 grams with an IV input target of zinc 160 mcg/kg/day in TPN over approximately 3-4 weeks (9) concluded that a higher zinc dosage of 200 mcg/kg/day was appropriate in this population.
- A study that randomized premature infants 28 to 31 weeks of gestational age to zinc doses varying from 40 mcg/kg/day to 400 mcg/kg/day for 2 weeks (10) found that serum zinc concentrations were maintained only in the 400 mcg/kg/day group.
- A study of preterm infants with mean weight of 0.9 kg and 27.5 weeks gestation receiving either enteral feeding exclusively or PN with zinc 350 mcg/kg/day for 3-4 weeks (11) found that this dosage maintained serum zinc concentrations.
- A study of low birthweight preterm infants receiving zinc 270 to 280 mcg/kg/day until full oral feeding volumes obtained (13) concluded that this dose was insufficient as it led to decreasing serum zinc concentrations.

Based on the collective evidence, the safety and effectiveness of Zinc Sulfate Injection have been established, and the dosing regimen (shown below) is recommended.

- The dosage of Zinc Sulfate Injection should be individualized based on the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral zinc intake.

Adults

The recommended adult dosage is 3 mg/day for metabolically stable patients, with potential need for a higher daily dosage in monitored patients with small bowel fluid loss and excess stool or ileostomy output.

Pediatric Patients

The recommended pediatric dosage is shown in the table below by age and estimated weight. The dosages in the table below are general recommendations intended for most pediatric patients. However, based on clinical requirements, some patients may require a higher dosage.

Recommended Dosage of Zinc Sulfate Injection for Pediatric Patients by Age and Estimated Weight

Population	Estimated Weight for Age	Recommended Daily Dosage
Pediatric patients	10 kg and above	50 mcg/kg (up to 3 mg/day)
	5 kg to less than 10 kg	100 mcg/kg
Term neonates	3 kg to less than 5 kg	250 mcg/kg*
Preterm neonate	Less than 3 kg	400 mcg/kg

*Term neonates have higher requirements in the first 3 months of life

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Unmet medical need: Approximate 40,000 patients in the U.S. use PN, and zinc trace element is an essential supplement of the PN. • Daily loss of zinc needs to be replenished: Excretion of zinc from the body is through the intestinal tract, largely in meal-stimulated	Substantial evidence supports that homeostatic regulation of zinc metabolism is achieved primarily through a balance of absorption and secretion of zinc trace element.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	pancreatic secretions. Endogenous zinc loss of 0.5 to 1.5 mg/day from desquamation of epidermal cells and sweating, and 0.5 mg/day from urine. • Stress, acute trauma, and infection cause changes in hormone (e.g., cortisol) and cytokines (e.g., interleukin) that lower plasma zinc (12) concentrations. • Mild zinc deficiency includes alopecia, diarrhea, growth retardation, delayed sexual maturation, eye and skin lesions and skeletal myopathy. Severe zinc deficiency is life-threatening.	Parenteral zinc is used to maintain the balance.
Current Treatment Options	• Zinc Chloride Injection, USP, 1 mg/mL IV (Approved on 2/14/2003; NDA 018959; Hospira). • Marketed, unapproved Zinc Sulfate Injection 5 mg/mL.	There is currently no marketed, approved zinc sulfate injectable product that meets the FDA quality standards for drug approval . Zinc chloride injection is an alternative. However, available products have been on the drug shortage list periodically since 2012.
Benefit	• Parenteral zinc supplementation has been shown to increase or maintain serum levels of zinc in the normal range. • However, plasma/serum zinc concentrations do not always accurately reflect total body zinc concentrations of zinc	In addition to monitoring of zinc concentrations, it is recommended to monitor for signs and symptoms of zinc deficiency during treatment, especially in pediatric patients.
Risk and Risk Management	• No deaths or other serious adverse events reported in clinical trials or postmarketing with injectable zinc sulfate were considered to be adverse reactions related to zinc administration No risk management plan is recommended.	No new safety signals are anticipated postmarketing. Routine pharmacovigilance is recommended.

1.4.Patient Experience Data

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

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

2 Therapeutic Context

2.1. Analysis of Condition

2.1.1. Parenteral Nutrition

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

PN can be used short-term or long-term in the hospital or home settings and may be used as the exclusive means to deliver nutrition or in combination with some amount of oral/enteral intake. According to the 2014 National Inpatient Survey data, over 290,000 patients received PN during their hospital stay and about 43% of those patients were newborns and children (13). It is estimated that about 25,000 patients receive PN at home (14).

2.1.2. Zinc

TEs are essential components of complexes required for fundamental processes such as enzymatic reactions. Some TEs are well-established as essential in human physiology, while others' roles and requirements have yet to be defined. Zinc is an essential trace element naturally present in many foods and is a constituent of various enzymes responsible for DNA replication, RNA transcription, and protein synthesis.

Zinc is obtained primarily through diet and the amount of zinc available in a diverse diet is typically sufficient to negate the need for additional supplementation. The precise zinc content in foods can vary greatly depending on where the produce is grown or produced. In the U.S., the estimated daily zinc intake for adults is approximately 13 mg/day (15). Deficiency in dietary zinc has been linked to certain clinical conditions, including loss of appetite, growth retardation and sexual immaturity, skin changes, diarrhea, loss of appetite, hair loss and immunologic abnormalities (15).

Case reports of zinc deficient PN patients were published starting in the 1970s and 1980s: dermatitis [1976 (12 cases total), 1978 (1 case total), 1978 (1 case total), 1985 (2 cases total)] and acrodermatitis enteropathica [1985 (1 case total)] (16-23). Descriptive studies evaluating zinc supplementation in PN were published starting in the 1970s and 1980s (9, 24-27). Non-randomized studies in patients on PN containing variable amounts of zinc were published starting in the 1970s and 1980s (5, 28).

In 1979, the Nutrition Advisory Group (NAG) of the Department of Food and Nutrition and the American Medical Association recommended that 4 TEs, zinc, copper, manganese, and chromium, be provided in adult PN formulas (29, 30). The recommended dosage of zinc was 2.5 to 4 mg/day. Subsequently, in 1984, 1994, 1998, and 2004, the recommended dosage for adults did not change considerably (31-34).

These recommendations were reviewed by the American Society for Parenteral and Enteral Nutrition (ASPEN) in 2009, 2012, and 2019 (1, 35, 36). Current ASPEN recommendations for adults are zinc **3-5 mg/day** (36).

2.1.3. Recommended Oral Intake

The Dietary Reference Intake (DRI), developed by the Food and Nutrition Board at the Institute of Medicine (IOM) of the National Academies (formerly National Academy of Sciences) {Institute of Medicine Panel on Dietary, 2000 #244}, is a general term used to describe a set of reference values used for planning and assessing nutrient intakes of healthy people, which can vary based on age and sex (37), and include the following:

- Estimated Average Requirement (EAR): Average daily level of intake estimated to meet the requirements of 50% of healthy individuals; usually used to assess the nutrient intakes of groups of people and to plan nutritionally adequate diets for them; can also be used to assess the nutrient intakes of individuals.
- Adequate Intake (AI): Intake at this level is assumed to ensure nutritional adequacy; established when evidence is insufficient to develop a Recommended Dietary Allowance (RDA).
- Tolerable Upper Intake Level (UL): Maximum daily intake unlikely to cause adverse health effects.
- Recommended Dietary Allowance (RDA): Average daily level of intake sufficient to meet the nutrient requirements of nearly all (97% to 98%) healthy individuals; often used to plan nutritionally adequate diets for individuals.

EAR

Calculation of the EAR for zinc was generally based on a factorial analysis (38), according to the following steps (38): (1) calculation of endogenous losses of zinc via routes other than the intestine; (2) relationship between excretion of endogenous zinc via the intestine and quantity of zinc absorbed; (3) determination of minimal zinc absorption required to replace total endogenous zinc excretion; and (4) determination of the average zinc intake required to achieve absorption of the quantity of zinc necessary to match total endogenous losses.

For age 19 years and above, the EAR for zinc was determined to be 9.4 mg/day for males and 6.8 mg/day for females (38). For age 19 years through 50 years, the EAR for zinc was based on a factorial analysis (38). For age ≥51 years, the EAR for zinc was based on extrapolation of factorial data from 19 years through 50 years (38).

For children and adolescents between the ages of 7 month through 18 years, the EAR was also based on a factorial analysis, and was determined to range between 2.5 mg/day and 8.5 mg/day .

There is an increased requirement during pregnancy ranging from 9.5 to 10.0 mg/day, and an increased requirement during lactation ranging from 10.4 to 10.9 g/day.

AI

The AI of 2 mg/day in infants ages 0 through 6 months is based on zinc concentration of human milk (2.5 mg/L) and the standard volume of milk intake (0.78 L/day). Using a similar method of calculation, the AI for infants ages 7 through 12 months is estimated to be 20 mcg/day or 2 mcg/kg/day.

RDA

The RDA for zinc is set by using a coefficient of variation (CV) of 10 percent (38). The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, the zinc RDA is 120 percent of the EAR) (38). The calculated RDA is rounded to the nearest 1 mg (38).

For age 19 years and above, the RDA for zinc was determined to be 11 mg/day for males and 8 mg/day for females (38).

For children and adolescents between the ages of 7 month through 18 years, the RDA was determined to be between 3 and 11 mg/day (38).

For infants ages 0 through 6 months, the RDA was determined to be 3 mg/day.

RDI

The value established by the FDA for use in nutrition labeling is the RDI. The RDI is based on the highest RDA for each nutrient, to assure that needs were met for all age groups. For the purpose of nutritional labeling, 21 CFR 101.9 established the RDI of Zinc to be 3 mg/day in children up to age 3 years; 11 mg/day in adults and children 4 years of age and greater; and 13 mg/day in pregnant and lactating females (39). The current RDI for zinc is summarized in the 2016 Final Rule – Food Labeling: Revision of the Nutrition and Supplementation Facts Label (40).

UL

The Tolerable Upper Intake Level (UL) for adults is 40 mg/day, a value based on reduction in erythrocyte copper-zinc superoxide dismutase activity (38). In addition, UL was calculated for infants as 4 mg/day for 0 to 6 months of age, and 5 mg/day for 7 to 12 months of age. UL for children/adolescents was calculated as 7 mg/day for 1 to 3 years of age, 12 mg/day for 4 to 8 years of age, 23 mg/day for 9 to 13 years of age, and 34 mg/day for 14 to 18 years of age (38).

Estimated Relative Bioavailability of Oral to Intravenous Zinc

The RDI and the UL represent the oral/enteral intake of zinc. These calculations by the IOM represent the daily dosage of absorbed zinc. Zinc absorption from the gastrointestinal tract following oral administration of zinc is homeostatically regulated, involving passive diffusion and a carrier-mediated process in the intestinal lumen (Cousins RJ. Physiological Reviews, 1985) (41). As summarized by the data below, the bioavailability of oral zinc can be estimated as approximately 30%. The bioavailability of Zinc Sulfate Injection is presumed to be 100%.

- Zinc uptake from a normal diet normally ranges from 26 to 33% (Sandstrom and Abrahamson, 1989 (42); Knudsen et al., 1995(43); Hunt et al., 1998 (44)) when taken with food, but is higher (i.e. 68 to 81%) in fasting conditions (Istfan et al., 1983 (45); Sandstrom and Abrahamson, 1989 (42)).
- Within a 5 to 25 mg dose range, zinc absorption, expressed as a percent of the total dose administered, decreases with dose. In healthy subjects, 61% of a 24.5 mg dose of zinc (as zinc chloride) was absorbed, compared to 81% of a 4.5 mg dose (45).
- The absorption of oral zinc is reduced by plant products containing phytate (46, 47). When 2.34 g of phytate as sodium phytate was added to a basal diet, zinc absorption fell from 34% to 17.5% (47).
- Zinc absorption is also affected by the amount and source of protein ingested (48, 49). Ingestion of zinc complexed with histidine increased zinc uptake and serum concentration compared with oral administration of zinc sulfate (50).
- Oral zinc absorption in infants was similar to that in adults. The mean zinc absorption was 31.1% and 28.6% in 11 nine-month-old infants receiving a commercial vegetable-based weaning food fortified and unfortified with iron, respectively (51). In another study, the mean absorption of zinc was approximately 50% in 16 infants 5 to 7 months old who received the mother's breast milk (52).

2.1.4. Deficiency

Low zinc nutritional status can result from diminished zinc content in the diet. In addition, deficiencies may occur due to inappropriate administration of micronutrients during PN or because of increased requirements or increased bodily losses. Zinc deficiency is defined as insufficient zinc in the body to maintain the physiological functions. Normal serum zinc is 0.66 to 1.10 mcg/mL (53).

The mean rate of zinc deficiency in 30 high-income countries (including the United States) has been estimated as 7.5% (12).

- For mild zinc deficiency, detectable symptoms and laboratory abnormalities are non-specific: e.g., alopecia, diarrhea, growth retardation, impaired wound healing, delayed sexual maturation and impotence, eye and skin lesions, and loss of appetite (54-56).

- Zinc deficiency may be life-threatening in infants and children. It can cause impaired immune function (IL-1β, IL-2, IL-6, and TNF-α), leading to infection, failure to thrive and growth retardation. Zinc deficiency is also associated with skin lesion, alopecia, taste disorders, loss of appetite, diarrhea, pneumonia, and neuropsychiatric changes (57-60).

Zinc diagnostic tests

Serum zinc concentrations along with clinical signs and symptoms are used to determine if a patient has zinc deficiency. Although good at detecting major deficiencies, serum zinc is insensitive to marginal zinc deficiency because a change in serum zinc does not occur until zinc intake is extremely low.

2.2. Analysis of Current Treatment Options

FDA-approved products

- Zinc Chloride Injection (Hospira), USP, 1 mg/mL IV (NDA 18959, approved on 6/26/1986)
  - See recommended dosing from labeling (61):

    For the metabolically stable adult receiving TPN, the suggested intravenous dosage is 2.5 to 4 mg zinc/day (2.5 to 4 mL/day). An additional 2 mg zinc/day (2 mL/day) is suggested for acute catabolic states. For the stable adult with fluid loss from the small bowel, an additional 12.2 mg zinc/liter of small bowel fluid lost (12.2 mL/liter of small bowel fluid lost), or an additional 17.1 mg zinc/kg of stool or ileostomy output (17.1 mL/kg of stool or ileostomy output) is recommended.

    Frequent monitoring of zinc blood levels is suggested for patients receiving more than the usual maintenance dosage level of zinc.

    For full term infants and children up to 5 years of age, 100 mcg zinc/kg/day (0.1 mL/kg/day) is recommended. For premature infants (birth weight less than 1500 g) up to 3 kg in body weight, 300 mcg zinc/kg/day (0.3 mL/kg/day) is suggested.
  - NDA 18959/S-008 and S-011, Abbott Laboratories, approved on 2/14/2003.
- Zinc Sulfate Injectable, EQ 1 mg/mL (Abraxis Pharm, NDA 019229, approved on 5/5/1987, withdrawn from market), USP, 4.39 mg (equivalent to Zinc 1 mg IV)
  - 2.5 to 4 mg/day for the metabolically stable adult
  - An additional 2 mg zinc/day is suggested for acute catabolic states. For the stable adult with fluid loss from the small bowel, an additional 12.2 mg zinc/liter of small bowel fluid lost, or an additional 17.1 mg zinc/ kg of stool or ileostomy output is recommended.
  - 100 mcg/kg/day for full-term infants and children up to 5 years of age
  - 300 mcg /kg/day for premature infants (birth weight less than 1500 grams) up to 3 kg

Marketed unapproved products

- Zinc Sulfate Injection, 1 mg/mL (American Regent, Inc., formerly known as Luitpold Pharmaceuticals)
    - See recommended dosing from labeling:

      For metabolically stable adults receiving TPN, the suggested intravenous dosage is 2.5 to 4 mg zinc/day. An additional 2 mg zinc/day is suggested for acute catabolic states. For the stable adult with fluid loss from the small bowel, an additional 12.2 mg zinc/liter of small bowel fluid lost, or an additional 17.1 mg zinc/kg of stool or ileostomy output is recommended. Frequent monitoring of zinc blood levels is suggested for patients receiving more than the usual maintenance dosage level of zinc.

      For full term infants and children up to 5 years of age, 100 mcg zinc/kg/day is recommended. For premature infants (birth weight less than 1500 g) up to 3 kg in body weight, 300 mcg zinc/kg/day is suggested.
- Multitrace-5 (MTE-5) (1 mg/mL zinc in a 10-mL multidose vial) and MTE-5 concentrate (5 mg/mL zinc in a 1-mL single-dose vial and 10-mL multidose vial). This is a fixed-combination product containing 5 trace elements (chromic chloride, cupric sulfate, manganese sulfate, selenious acid, and zinc sulfate heptahydrate).

Both products are manufactured by American Regent.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Zinc Sulfate Injection seeks the 505(b)(2) regulatory pathway for FDA approval. The Applicant currently markets an unapproved Zinc Sulfate Injection product. In the past, injectable zinc has been considered a drug-shortage product by the FDA Drug Shortage program; it is not currently in shortage.

See Section 2.2 Analysis of Current Treatment Options regarding marketed, unapproved zinc parenteral products.

3.2. Summary of Presubmission/Submission Regulatory Activity

Since 2009, ASPEN has been in communication with the Division of Gastroenterology and Inborn Errors Products (DGIEP) on multiple occasions due to concerns relating to lack of approved PN products, drug shortages and marketed unapproved products. ASPEN has urged the Agency to approve safe and effective injectable TE products (including zinc) that comply

with the current standards of clinical practice, fulfill the Agency's quality standards, and meet the supply and demand of the market.

(b) (4)

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

4.1.Office of Scientific Investigations

An Office of Scientific Investigations audit was not requested or performed given that the Applicant did not conduct any clinical trials.

4.2.Product Quality

The active ingredient, zinc sulfate, USP is manufactured as (b) (4) It is very soluble in water and insoluble in alcohol. Its empirical formula is $ZnSO_4.7H_2O$ and its molecular weight is 287.56.

Zinc sulfate, USP is manufactured by (b) (4). The complete CMC information regarding raw materials, manufacturing, purification, characterization, stability, storage and container closure is provided in DMF (b) (4).

The overall quality of zinc sulfate, USP is controlled by its specification. The specification is consistent with the USP monograph of zinc sulfate, USP. The particle size and polymorphs of zinc sulfate, USP are not important because the drug product is an injection. The drug substance manufacturing process, specification and stability data are deemed adequate per drug substance reviewer. The API manufactured by (b) (4) is controlled to conform to the requirements (specification) to produce Zinc Sulfate Injection, USP.

Zinc Sulfate Injection, supplied as 3 mg/mL of zinc and 5 mg/mL of zinc is a sterile, non-pyrogenic, clear, colorless and odorless (b) (4) solution for use as a source for trace element and an additive to PN. In the case of the 30 mg/10 mL vial, each mL of solution contains 3 mg of zinc as 7.41 mg of zinc sulfate. In the case of the 25 mg/5 mL vial, each mL of solution contains 5 mg of zinc as 12.32 mg of zinc sulfate. The pH of the (b) (4) solution is adjusted between 2 to 4 with sulfuric acid. There are no preservatives or antioxidants in the drug product formulation.

The drug product is manufactured by American Regent, Inc., NJ (formerly Luitpold Pharmaceuticals, Inc.). The manufacturing process includes: (b) (4). The drug product manufacturing process and microbiology related sections were reviewed and deemed adequate for manufacturing process robustness and sterility assurance.

The Applicant confirmed that potential leachables, e.g., (b) (4) levels are below the permitted daily exposure (PDE). Aluminum content is controlled to NMT 2500 mcg/L. The vials were tested for compatibility per USP <660> and met compendial requirements. Based on the admixture in-use stability study, the drug product appeared to be compatible with Kabiven and Clinimix E solutions.

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

The Office of Process and Facilities (OPF) has made an "Adequate" recommendation for all facilities in this application.

A claim for a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31 is granted.

The labels and labeling are deemed satisfactory from the CMC perspective.

Therefore, from the Office of Pharmaceutical Quality perspective, this NDA is recommended for **approval** with an expiration dating period of 24 months.

4.3.Clinical Microbiology

The environmental monitoring (b) (4) as well as the microbiology-related attributes of the drug product specification, including bacterial endotoxins, sterility and container closure integrity, etc., were reviewed and deemed adequate. Therefore, this NDA is recommended for approval based on drug product sterility assurance.

4.4.Devices and Companion Diagnostic Issues

No companion device or diagnostic was included in this NDA.

5 Nonclinical Pharmacology/Toxicology

5.1.Executive Summary

No nonclinical studies have been conducted by the Applicant with Zinc Sulfate Injection, and the Applicant is relying on published literature to support a 505(b)(2) NDA for Zinc Sulfate Injection.

Limited literature data exists to assess the toxicity of intravenously administered zinc or zinc sulfate. Zinc absorption after oral administration in animals mostly occurs in the duodenum, followed by the ileum. Zinc distributes throughout the body but highest concentrations are found in the bone, muscle, prostate, liver, and kidneys. Metabolism of zinc does not occur, as it exists as a divalent cation. Zinc is eliminated mostly via the feces, followed by urine. Other routes of elimination include sweat, salivary secretions, and incorporation into hair.

No toxicology data were identified in the literature with intravenously administered zinc sulfate or zinc-containing compounds. In repeated-dose toxicity studies where rodents were orally administered zinc-containing compounds, the major targets of zinc toxicity were blood, kidneys, pancreas, and the gastrointestinal tract. The mutagenicity findings of zinc are equivocal, though zinc is likely a clastogen. Zinc sulfate is not considered to be mutagenic, and has not been evaluated for clastogenicity. The carcinogenic potential of zinc and zinc-containing compounds cannot be determined due to the lack of adequately conducted animal studies. Excess zinc has the potential to be a reproductive toxicant. Zinc-containing compounds arrested spermatogenesis and induced necrosis of Sertoli and Leydig cells in male rats, decreased conception and live births in female rat, and reduced fetal weight/growth in juvenile rats. In juvenile rats, zinc-containing compounds also induced copper deficiency. However, these effects were observed at doses ≥110x the ~~highest~~ recommended clinical dose (up to 3 mg/day), and are, therefore, considered unlikely to be a risk for patients at the proposed dose.

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

5.2.Referenced NDAs, BLAs, DMFs

None.

5.3.Pharmacology

Zinc is required for nucleic acid, protein, and membrane metabolism, as well as maintenance of genetic nucleic acid structures (zinc finger phenomenon), cell growth, and cell division. Zinc is a

cofactor for many enzymes, including alcohol dehydrogenase, alkaline phosphatase, carbonic anhydrase, leucine aminopeptidase, superoxide dismutase, lactic dehydrogenase, and both RNA and DNA polymerases (62). No studies have been reported in the literature that evaluated the cardiovascular toxicity of intravenous or oral exposure to zinc.

5.4.ADME/PK

Type of Study	Major Findings
Absorption *(63) EPA IRIS for Zinc, 2005; (62) ATSDR for Zinc*	• 40-48% oral absorption in rats. 60% of absorption occurs in duodenum, 30% in ileum. • 26-33% (fed) and 68-81% (fasted) oral absorption in humans. • Zinc is absorbed from the intestinal lumen via passive diffusion and a carrier-mediated process.
Distribution *(63) EPA IRIS for Zinc, 2005; (64)Ansari et al., 1975; (62) ATSDR for Zinc*	• Distributes to all tissues. Highest concentrations are found in heart, spleen, blood, bone, muscle, prostate, liver, and kidneys. • Highly bound to plasma proteins, specifically albumin.
Metabolism (63) *EPA IRIS for Zinc, 2005*	• Zinc does not undergo metabolism.
Excretion (63) *EPA IRIS for Zinc, 2005; (62) ATSDR for Zinc*	• Primarily excreted via feces (70-80%), followed by urine. • Other routes of elimination include sweat, saliva secretion, and incorporation into hair.

5.5.Toxicology

5.5.1. General Toxicology

No available studies have assessed the toxicity of Zinc Sulfate Injection or intravenously administered zinc or zinc sulfate. The toxicology information of orally administered zinc sulfate and zinc-containing compounds is used to inform the potential toxicity of intravenously administered zinc sulfate. The major targets of zinc toxicity are blood (hemoglobin, hematocrit, erythrocyte, and/or leukocyte levels), kidneys, spleen, pancreas, and the gastrointestinal tract (63).

In a published 13-week toxicity study, ICR mice (n=12/sex/group) were fed a diet supplemented with zinc sulfate at 0, 300, 3,000, and 30,000 ppm (equivalent to 44.6, 469, and 4900 mg/kg/day)(65). Four males and one female in the 4900 mg/kg/day group were found dead or euthanized *in extremis.* Decreased motility and unkempt fur were observed in these animals, and histopathology evaluation revealed impairment of the urinary tract and degenerative changes in the exocrine gland of the pancreas. No adverse clinical signs were observed in surviving animals. Decreased food consumption (-44%) was observed in the 4900 mg/kg/day males and females during the first week of the study compared to controls, but recovery

occurred through the remainder of the study. Body weights initially decreased in the 4900 mg/kg/day group, correlating with decreased food consumption during this time. By Week 2 and continuing throughout the study, body weight gain was similar in males compared to controls. In females, body weight gain was similar to controls from Week 2 to Week 6, but decreased compared to controls thereafter. No changes in food consumption or body weight were observed in the 44.6 or 469 mg/kg/day groups. Zinc sulfate at 4900 mg/kg/day decreased hematocrit (-30%), hemoglobin (-30%), and red blood cell (-26%) levels in males and females, and decreased leukocyte counts (-25%) in males, compared to controls. Total protein was also slightly decreased 6 to 15% in the 4900 mg/kg/day groups compared to controls, while alkaline phosphatase (75 to 112%) and urea nitrogen (32 to 43%) increased. Following necropsy, discoloration of the kidney and thyroid, pancreatic atrophy, edematous thickening of the small intestine, forestomach ulcers, and splenomegaly were observed in 4900 mg/kg/day males and females. Relative kidney (74%) and thyroid (57%) weights were increased in the 4900 mg/kg/day females and males, respectively, compared to controls. These changes did not correlate with histopathological findings. Histopathological changes in the 4900 mg/kg/day group were observed in the pancreas (acinar cell: swollen nuclei, increased basophilic cytoplasmic infiltrates, decreased acinus and ductule-like metaplasia, and single cell necrosis), small intestine (mucosal buildup, proliferation of epithelial cells, and edema at lamina propria), forestomach (ulcerative lesions), spleen (immature erythropoietic cells in red pulp), and kidney (degenerative changes in renal cortex, not specified). The incidences of these lesions were not reported. The no observable adverse effect level (NOAEL) is 469 mg/kg/day, 9380x higher than the recommended clinical dose (up to 3 mg/day). It should be noted that the 4900 mg/kg/day dose is far higher than the recommended clinical dose, and, thus, the adverse findings observed at this dose are not relevant to humans.

In a published 13-week toxicity study, Wistar rats (n=12/sex/group) were fed a diet supplemented with zinc sulfate at 0, 300, 3,000, and 30,000 ppm (equivalent to 23.9, 239, and 2500 mg/kg/day) (65). No treatment-related mortalities or adverse clinical signs were observed in this study. Of note, beginning 1 week after treatment initiation and continuing throughout the study, males and females in the 2500 mg/kg/day groups began picking food out of the food jar with their forelimbs and discarding it. This behavior correlated with a 5 to 15% decrease in food consumption and may indicate that the food was not palatable. Body weight gain was decreased in the 2500 mg/kg/day males and females compared to control throughout the study; males were more severely affected. Zinc sulfate at 2500 mg/kg/day decreased leukocyte counts in males (-36%) and females (-26%). No other treatment-related effects on hematological parameters were observed. Aspartate aminotransferase and alanine aminotransferase were decreased 12.6% and 24%, respectively, in the 2500 mg/kg/day males compared to controls, but not in females. No other treatment-related effects on serum biochemistry parameters were observed. Following necropsy, no treatment-related macroscopic findings were observed. Relative liver weights were decreased 10% in 2500 mg/kg/day males compared to controls. No treatment-related effects on relative organ weights were observed in females, and this change in males was not correlated with histopathological findings. Histopathological changes in the 2500 mg/kg/day group were limited to the pancreas

(acinar cells: swollen nuclei, increased basophilic cytoplasmic infiltrates, decreased acinus and ductule-like metaplasia, single cell necrosis, degeneration and necrosis; centroacinar cells: clarification; interstitium: fibrosis). The incidences of these lesions were not reported. The NOAEL is 239 mg/kg/day, 4780x higher than the recommended clinical dose (up to 3 mg/day). It should be noted that the 2500 mg/kg/day dose is far higher than the recommended clinical dose, and, thus, the adverse findings observed at this dose are not relevant to humans.

In mice fed a diet containing zinc at 76.9 mg/kg/day (zinc sulfate) for 4 weeks, then challenged with B cell antigens *in vitro* or *in vivo,* no effect was observed on antibody titer (IgG or IgM) or the mitogenic response of splenic isolated B cells (66). There was no effect of the zinc supplement in the plaque forming cell assay or on cytotoxic T-killer cell activity in mice exposed to 6.5 mg zinc/kg/day in the diet for 8 weeks (67).

5.5.2. Genetic Toxicology

The genotoxicity of zinc sulfate has not been fully characterized. However, the genotoxicity findings of zinc are considered equivocal (62, 63), though zinc is likely a clastogen. Responses in mutagenicity assays appear to depend on the form of the zinc tested (63). In published literature, zinc sulfate was not considered to be mutagenic in an Ames test and mouse microsome assay, though zinc acetate and zinc chloride have been reported positive in the Ames test (62). Zinc chloride has been reported positive in mouse lymphoma and human lymphocyte assays, whereas zinc acetate was positive in a mouse lymphoma assay and *in vivo* micronucleus assay in rats, but negative in human lymphocyte assays (63, 68).

5.5.3. Carcinogenicity

Adequate animal studies to evaluate the carcinogenic potential of zinc have not been conducted and are not available in the literature. The deficiencies in the available literature, described below, preclude a definitive determination of the carcinogenic potential of Zinc Sulfate Injection.

In a 1-year study, newborn Chester Beatty mice (sex not reported) were exposed to zinc sulfate in drinking water at 0, 170, or 850 mg/kg/day. Survival was not reported in treatment groups compared to controls. The incidence of hepatoma was slightly increased in the 850 mg/kg/day group (7 of 23) compared to controls (3 of 24). The incidence of malignant lymphoma and lung adenoma were similar in treatment and control groups. No further information is available (63).

In a 3-year, 5-generation study, “tumor-resistant” (strains not reported) and “tumor susceptible” mice (strains reported as C3H and A/Sn) mice were exposed to zinc chloride in drinking water at 0, 10, 20, 50, 100, or 200 mg Zn/L (1.25, 2.5, 6.25, 12.5, or 25 mg/kg/day). The tumor frequency for the tumor-resistant mice was 0.0004%. Neither individual nor group tumor incidence data were reported. In the tumor-susceptible mice, 33 of 76 C3H mice developed tumors, mainly in females, and 24 of 74 A/Sn mice developed tumors, mainly in males. The overall tumor frequencies (43.4% for C3H and 32.4% for A/Sn, sex-combined) were reportedly

higher than the spontaneous frequency for each strain (15%), though no statistical analyses were provided. Most tumors were reported to be adenocarcinomas, though the number of specific tumor types and the tissues in which they occurred were not provided (63). However, tumor susceptible strains of mice are not traditionally used in carcinogenicity assessments. Therefore, these data do not provide reliable information on the carcinogenic potential of zinc-containing compounds.

5.5.4. Reproductive and Developmental Toxicology

The reproductive and developmental toxicity of zinc appears to depend on the form of the zinc tested. Few reproductive or developmental toxicity studies have been conducted with zinc sulfate. Based on the available data, zinc has the potential to arrest spermatogenesis and induce necrosis in Sertoli and Leydig cells in male rats, reduce conception and live births in female rats, and reduce fetal weight/growth in juvenile rats. However, as noted in each study summary below, these adverse findings were observed at doses far higher than the recommended clinical dose (up to 3 mg/day). Thus, the adverse findings observed at these doses are not relevant to humans.

Reproductive Toxicity

In male rats fed a diet supplemented with zinc at 28 mg/kg/day (unspecified form of zinc) for 3 or 6 weeks, alopecia was observed, indicating a copper deficiency (63). No significant effects on reproductive tissues were observed, but enzyme activities within male reproductive tissues were altered. Lactic dehydrogenase activity was decreased after 3 and 6 weeks, and arylsulfatase and leucyl aminopeptidase activities were increased. Histopathological findings after 3 weeks included meiotic arrest at the primary spermatocyte stage, degenerating secondary spermatocytes, fluid accumulation within the seminiferous tubules, and reduced epithelial height in the epididymis. Further evidence of arrested spermatogenesis (one layer of primary spermatocytes, germinal epithelium with only spermatogonia, no mature spermatozoa in the cauda epididymis) was observed after 6 weeks. Necrotic nuclei in Sertoli cells, Leydig cells, and epithelia of prostatic follicles and seminal vesicles were also observed. In another study, abnormalities in the chromosomal structure of sperm were observed after male rats were fed a diet supplemented with zinc at 49 mg/kg/day (unspecified form of zinc) (63). The adverse effects observed in these studies occurred at doses 560x-980x higher than the recommended clinical dose. Exposure to zinc at 8 mg/kg/day (zinc acetate; 160x higher than the recommended clinical dose) every other day for 14 days showed no significant effect on the levels of abnormal sperm in Wistar rats compared to controls (62, 68).

A group of 12 female rats were fed a diet supplemented with zinc at 450 mg/kg/day (zinc sulfate) for 18 days immediately after coitus. Conception was reduced in Zn-fed females (5 of 12) compared to controls (12 of 12). Implantation sites were not affected in the Zn-fed females that did conceive (5 of 12). Zinc also had no effect on the number of resorption sites, live births, or fetal development (63, 69). In another study in which 12 female rats were fed a diet supplemented with zinc at 20 mg/kg/day (zinc sulfate), no alterations in the implantation sites were observed, but the number of resorptions increased 9.5% compared to controls (63). The

adverse effects observed in these studies occurred at doses 400x-9000x higher than the recommended clinical dose.

Female (n=3/group) and male (n=2/group) rats were fed diets supplemented with zinc at 0, 113, 565, or 1130 mg/kg/day (unspecified form of zinc) for 10-39 weeks. Some rats in the 1130 mg/kg/day groups died and were observed with reduced growth (no data provided). No reproduction occurred in this group. Stillbirths and dead fetuses were observed in the 565 mg/kg/day group, and the females failed to become pregnant again after 5 months. Normal reproduction was observed in the 113 mg/kg/day groups (63). The adverse effects observed in this study occurred at doses 11,300x-22,600x higher than the recommended clinical dose.

In a study in which female rats were fed a diet supplemented with zinc at 200 mg/kg/day (zinc oxide) for 21 days prior to mating and during gestation, 100% fetal resorption was observed. No fetal resorptions were observed in rats fed a diet supplemented with zinc at 100 mg/kg/day (zinc oxide). When zinc at 200 mg/kg/day was supplemented in the diet only during gestation, fetal resorptions occurred but at a lesser incidence (4 to 29%). No external malformations were observed in this study (62, 63). The adverse effects observed in this study occurred at a dose 4000x higher than the recommended clinical dose. Conversely, no fetal resorptions or other effects on reproductive performance were observed in female rats fed a diet supplemented with zinc at 250 mg/kg/day (zinc carbonate) for 53 days before mating and during gestation (62). In another study with zinc carbonate, no effect on fetal viability, size, or malformations were observed in fetuses from female rats fed a diet supplemented with zinc at 25 mg/kg/day (62).

Developmental Toxicity
Exposure to high levels of zinc in the diet (≥200 mg Zn/kg/day; ≥4000x the recommended clinical dose) prior to and/or during gestation has been associated with reduced fetal weights, alopecia, altered tissue concentrations of fetal iron and copper, and reduced growth in the offspring of rats (62, 63). Alopecia is likely a secondary result of zinc-induced copper deficiency (62, 63).

Juvenile Toxicity
In juvenile male Wistar rats (PND 21; n=10/group) fed a diet supplemented with zinc at ≥5.5 mg/kg/day, decreased liver copper levels, liver zinc-superoxide dismutase activity, and heart cytochrome c oxidase activity were observed. Heart copper levels, heart zinc-superoxide dismutase activity, and liver cytochrome c oxidase activities were not affected (63). These effects observed in this study occurred at doses 110x or higher than the recommended clinical dose.

5.5.5. Other Toxicology Studies

Safety Assessment of Elemental Impurities
The Applicant conducted a risk assessment of all Class 1, 2A, 2B, and 3 elemental impurities recommended in ICH Q3D. A risk assessment was also conducted for (b) (4)

[redacted]. The Applicant's specifications for elemental impurities are adequate per ICH Q3D. The Applicant's specification limits for [redacted] are appropriate and acceptable.

[redacted]
The calculation of the PDE for [redacted] was based on the NOAEL of [redacted] mg [redacted]/kg/day determined in an oral embryofetal developmental toxicity study in rabbits, as reported in the Agency for Toxic Substances and Disease Registry (ATSDR) for [redacted] (70). The bioavailability of [redacted] is [redacted]% in humans and [redacted]% in animals (rats). The calculated PDE of [redacted] mg/kg/day (shown below) is [redacted]x higher than the specification limit set for [redacted] Therefore, the Applicant's specification for [redacted] is acceptable.

PDE= [redacted] **mg/day**

F1 = 2.5 (rabbit to human)
F2 = 10 (individual variability)
F3 = 1 (reproductive study)
F4 = 10 (fetal teratogenicity with no maternal toxicity)
F5 = 1 (NOAEL was used)
F6 = 2 (≥50 and<90% bioavailability)

[redacted]
The tolerable upper intake levels (UL) of oral [redacted] for infants 0 to 6 months of age is [redacted] mg/day (71). The recommended UL of [redacted] in infants is 20,000x higher than the Applicant's specification limit [redacted] mcg/mL; [redacted] mcg/day). Thus, the Applicant's specification for [redacted] is acceptable.

[redacted]
The recommended dietary allowance and adequate intake (AI) of [redacted] in pediatric patients is [redacted] mg/day ([redacted] mcg/day) (72). The RDA and AI of [redacted] is 60-1500x higher than the specification [redacted] mcg/mL [redacted] mcg/day). Thus, the Applicant's specification for [redacted] is acceptable.

[redacted]
Adequate intake (AI) of [redacted] in patients aged 1 to ≥51 years old is [redacted] mcg/day (73). The AI of [redacted] is 21.3-36.2x higher than the specification [redacted] mcg/mL; [redacted] mcg/day). Thus, the Applicant's specification for [redacted] is acceptable.

[redacted]
The calculation for the PDE of [redacted] is based on the NOAEL of [redacted] mg/kg/day determined in a 3-month toxicity study in rats administered sodium silicate via drinking water, as reported in the OECD Screening Information DataSet (SIDS) on soluble silicates (74). The bioavailability of [redacted] is unknown, so an uncertainty factor of 10 was applied. The calculated PDE of [redacted]

mg/kg/day (shown below) is much higher than the specification limit set for [redacted] mcg/mL; [redacted] mcg/day). Therefore, the Applicant's specification for silicon is acceptable.

PDE= [redacted] **mg/day**

F1 = 5 (rat to human)
F2 = 10 (individual variability)
F3 = 5 (3-month study in rodents)
F4 = 1 (no severe toxicity)
F5 = 1 (NOAEL was used)
F6 = 10 (bioavailability unknown)

[redacted]
The recommended daily intake of [redacted] for children and adults is [redacted] g/day [redacted] mcg/day) (75). The RDI of [redacted] is 8.3x higher than the specificatio [redacted] mcg/mL; [redacted] mcg/day). Thus, the Applicant's specification for [redacted] is acceptable.

Safety Assessment of Aluminum

The Applicant's aluminum specification of 2500 mcg/L is acceptable for adult patients and pediatric patients ≥10 kg and <27 kg, based on the recommended daily clinical dose of up to 3 mg (i.e., 1 mL/day Zinc Sulfate Injection and a concentration of 3 mg/mL). At this specification, the daily patient exposure to aluminum will be <0.6 mcg/kg/day (adults: 0.04 mcg/kg/day; pediatric patients: 0.09 to 0.25 mcg/kg/day). As this is a small volume parenteral intended for use in a multi-component PN, this specification and daily exposure limit of aluminum should ensure the daily patient exposure from all potential sources of aluminum in the TPN admixture does not exceed 5 mcg/kg/day (76).

Safety Assessment of Extractables/Leachables

The known extractables from the [redacted] glass vial [redacted] and [redacted] stopper are [redacted]

The Applicant conducted leachables assessments using the reverse-phase high performance liquid chromatography/ diode array detection (HPLC-DAD) method and Total Organic Carbon (TOC) method on upright samples and inverted samples to represent the "worst-case" scenario due to product contact with the stopper. For both methods, samples had been stored at 25°C/60% relative humidity (RH) for 18 to 32 months (end of shelf life is 24 months). In five of six lot samples measured by the TOC method, total daily intake of organic leachables in Zinc Sulfate Injection (1 mL/day) was [redacted] mcg/day. In one sample 8 months past the expiration date (32 months), total daily intake of organic leachables was [redacted] mcg/day. No additional leachables were detected in the inverted samples compared to the upright samples, suggesting no leachables from the stopper were detected. As these leachables were detected at levels similar to or lower than the PQRI qualification threshold for mutagens/carcinogens in

parenteral products (1.5 mcg/day), there is no safety concern for the identified leachables. Overall, the leachable profile associated with the drug product container closure system appears to be acceptable.

6 Clinical Pharmacology

6.1 Executive Summary

Zinc is an essential trace element. The Applicant submitted a literature-based 505(b)(2) application for Zinc Sulfate Injection without conducting new clinical trials in the NDA.

Proposed Indication:

- A source of zinc for parental nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated in adults and pediatric patients.

FDA-recommended dosing regimens:
The dosage of Zinc Sulfate Injection should be individualized based on the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral zinc intake.

Adults
The recommended adult dosage is 3 mg/day for metabolically stable patients, with potential need for a higher daily dosage in monitored patients with small bowel fluid loss or excess stool or ileostomy output.

Pediatric Patients
The recommended pediatric dosage is shown in Table 1 by age and estimated weight. The dosages in Table 1 are general recommendations intended for most pediatric patients. However, based on clinical requirements, some patients may require a higher dosage.

Table 1: Recommended Dosage of Zinc Sulfate Injection for Pediatric Patients by Age and Estimated Weight

Population	Estimated Weight for Age	Recommended Daily Dosage
Pediatric patients	10 kg and above	50 mcg/kg (up to 3 mg/day)
	5 kg to less than 10 kg	100 mcg/kg
Term neonates	3 kg to less than 5 kg	250 mcg/kg*
Preterm neonates	Less than 3 kg	400 mcg/kg

*Term neonates have higher requirements in the first 3 months of life

Proposed dosage forms:

- 30 mg/10 mL (3 mg/mL) of zinc present as zinc sulfate in a Pharmacy Bulk Package vial
- 25 mg/5 mL (5 mg/mL) of zinc present as zinc sulfate in a Pharmacy Bulk Package vial

The key review findings with specific recommendations and comments are summarized in Table 2 below.

Table 2: Summary of Clinical Pharmacology of Zinc Sulfate Injection

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	• The dose-response relationship for improving serum zinc concentrations provides supportive evidence of effectiveness.
General dosing instructions	• The general dosage recommendations intended for most patients are based on patient's age (adults vs. pediatrics) and estimated body weight (among pediatric subjects).
Dosing in patient subgroups	• The dosage regimen is further individualized based upon the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral zinc intake.
Drug interactions	• There is a potential for drug interaction between zinc administered intravenously and copper hemostasis, leading to reduced copper absorption and deficiency. • If signs and symptoms of copper deficiency develop, interrupt treatment with Zinc Sulfate Injection and check zinc, copper, and ceruloplasmin levels. Copper deficiency should be treated with supplemental copper administration and discontinuation of zinc supplementation.
Therapeutic monitoring	• Monitoring of zinc concentrations and signs and symptoms of zinc deficiency is recommended during treatment, especially in pediatric patients. Plasma/serum zinc concentrations do not always accurately reflect total body zinc; therefore, the assessment of zinc status and requirements is also based on monitoring for signs and symptoms of zinc deficiency. (A clinical syndrome of acrodermatitis enteropathica consisting of scaly, red, desquamating lesions involving the nasolabial folds and hands. In severe cases it extends to the trunk, resulting in extensive exfoliation and secondary skin infection. There is often loss of hair.) (1) • Zinc concentrations may vary depending on the assay used and the laboratory reference range. • More than 75% of whole blood zinc is present in erythrocytes. Zinc concentrations in hemolyzed samples are falsely elevated due to release of zinc from the erythrocytes (77). • Samples collected with different collection tubes and anticoagulants result in different zinc concentrations due to zinc contaminants; therefore, collection of blood for analysis of zinc concentrations should be performed using collection tubes specifically designed to be zinc-free (78). • The collection, processing, and storage of blood samples for zinc analysis should be performed according to the laboratory's sample requirements. • The lower end of the reported range in healthy adults in plasma/serum is 60 mcg/dL. Observation of such a low zinc concentration during treatment warrants close monitoring of patients for signs and symptoms of zinc deficiency.

6.1.1. Recommendations

From a Clinical Pharmacology standpoint, the NDA is acceptable to support the approval of Zinc Sulfate Injection as a source of zinc for PN when oral or enteral nutrition is not possible,

insufficient, or contraindicated in adults and pediatric patients, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling.

6.2.Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of action and pharmacodynamics

Zinc is an essential trace element. It functions as a cofactor of various enzymes including DNA polymerases, RNA polymerases, alcohol dehydrogenase, and alkaline phosphatases. Zinc is a coordinator of protein structural folding, such as folding of "Zinc finger" motif that interacts with a variety of proteins, lipids, and nucleic acids. In addition, zinc is a catalyst of essential biochemical reactions, including activation of substrates of carbonic anhydrase in erythrocyte. Also, zinc is a signaling mediator modulating multiple signaling pathways.

Pharmacokinetics

Zinc is widely distributed in all tissues and tissue fluids; most of the total body zinc is in skeletal muscle and bone. Approximately 80% of serum zinc is bound to albumin and the remainder to α2-macroglobulin and amino acids. In adults, zinc is primarily excreted via the gastrointestinal tract and eliminated in the feces; a smaller amount of zinc is excreted via the kidneys in the urine. Urinary zinc excretion rates in very low birth weight preterm infants are relatively high in the neonatal period, and they decline to a level on a body weight basis that is similar to that of normal adults by 2 months of age. Other minor routes of elimination are sweat, saliva secretion, and incorporation into hair.

Drug interactions

There is a potential for drug interaction between zinc administered intravenously and copper hemostasis, leading to reduced copper absorption and deficiency.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Overall, the literature data support that the proposed doses for Zinc Sulfate Injection are reasonable. See Section 6.3.2 for more information.

Therapeutic Individualization

The general recommendations intended for most patients are based on patient's age (adults vs. pediatrics) and body weight (among pediatric subjects). However, based on clinical requirements, some patients may require a higher dosage. The dosage of Zinc Sulfate Injection should be further individualized based on the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral zinc intake.

Outstanding Issues
There are no outstanding issues that would preclude the approval of Zinc Sulfate Injection from a clinical pharmacology perspective.

6.3.Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology
Zinc is an essential trace element and is involved in catalytic, structural, and regulatory roles in the human body (79).

Zinc functions as a cofactor of various enzymes including DNA polymerases, RNA polymerases, alcohol dehydrogenase, and alkaline phosphatases. It catalyzes many essential biochemical reactions, including activation of substrates of carbonic anhydrase in erythrocyte and digestion of proteins by carboxypeptidase. Zinc is a Lewis acid; its action as an electron acceptor contributes to its catalytic activity in many of these enzymes.

Zinc is a coordinator of protein structural folding, such as folding of "Zinc finger" motif that interacts with a variety of proteins including transcription factors, lipids, and nucleic acids. These motifs use cysteine and histidine to form a tetrahedral Zn^{2+} coordination complex that helps maintain the finger's structure by coordinately binding to transcription factors.

Zinc is a signaling mediator modulating multiple signaling pathways. Metallothionein expression is regulated by a mechanism that involves zinc's binding to the transcription factor, metal response element transcription factor, which activates gene transcription (80, 81).

Absorption:
Zinc absorption is not applicable for Zinc Sulfate Injection because it is for intravenous injection.

Distribution
Distribution of zinc following intravenous administration of Zinc Sulfate Injection is expected to be similar to that of endogenous zinc.

Zinc is widely distributed in all tissues and tissue fluids. Eighty-six percent of the total body zinc is in skeletal muscle and bone (79). Other organs containing zinc are the liver, kidney, skin, brain, and heart (79). In blood, zinc is found in plasma, erythrocytes, leukocytes, and platelets but is mainly localized within erythrocytes (82). Approximately 80% of serum zinc is bound to albumin and the remaining to α2-macroglobulin and amino acids (83).

Metabolism
Zinc does not undergo metabolism, as it is a cation. Homeostatic regulation of zinc is controlled in part by regulating the efficiency of intestinal absorption and excretion from endogenous zinc pools (84) .

Excretion

In adults following oral intake, zinc is primarily excreted via the gastrointestinal tract and eliminated in the feces; the quantity of intestinal zinc loss is positively correlated with the quantity of zinc absorbed over a wide range (38). A smaller amount of zinc is excreted via the kidneys in the urine. In healthy subjects, 86% of the zinc lost from the body was secreted via the gut, whereas the remaining (i.e., 14%) was lost via excretion in urine (85). When zinc intake was increased, urinary excretion accounted for 25% of the zinc eliminated (85). Other minor routes of elimination are sweat (86), saliva secretion (87), and incorporation into hair (88). The biological half-life of radioactive zinc tracers was estimated to range from 300 to 450 days (89, 90).

In preterm infants with very low birth weight (<1500 g), urinary zinc excretion rates were found to be relatively high in the first 30 days. The rates then declined rapidly to a level that is similar on a body weight basis to that of normal adults by 60 to 62 days (91).

Presence of certain amino acids in PN has been shown to affect zinc hemostasis (92). In preterm and full-term infants receiving PN, urinary zinc excretion was elevated during infusion of high-dose histidine (mean: 140 to 152 mg/kg/day) and cysteine (mean: 78 to 83 mg/kg/day) compared with that during the no-cysteine and low-dose histidine (mean: 80 to 89 mg/kg/day). Varying histidine and cysteine intakes had no effect on plasma zinc concentrations. However, in an earlier study by the same author, urinary zinc excretion was similar when high histidine (mean: 124 mg/kg/day) and low histidine (mean: 85 mg/kg/day) was infused at rates appropriate for the safety and nutritional maintenance of neonates. Based on the highest histidine requirements of 36 mg/kg/day in pediatric subjects 0 to 6 months old (93), increased zinc loss via urine excretion is not expected in pediatric subjects receiving zinc dosage within the clinical requirements of histidine for the corresponding age group.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the dose-response relationship for improving serum zinc concentrations provides supportive evidence of effectiveness of Zinc Sulfate Injection. For example, administration of intravenous zinc in preterm neonates reversed the zinc concentration decline during PN in a dose-dependent manner, with a maximal effect observed at the highest zinc dose evaluated of 400 mcg/kg/day. On the other hand, zinc concentration decreased to below the lowest limit of normal in preterm neonates who received 40 mcg/kg/day intravenous zinc.

Zinc concentrations were evaluated in 96 preterm neonates with low birthweight <2000 g receiving PN over 7 weeks (10). Subjects were randomized to receive 100, 200, or 400 mcg/kg/day of zinc and either 20 or 40 mcg/kg/day of copper supplementation to the PN or the control group. The control group received standard supplementation of zinc 40 mcg/kg/day and copper 20 mcg/kg/day copper. Mean serum zinc concentrations at Week 1 were similar among

all dose groups. Mean zinc concentration across all treatment groups declined from 114 mcg/dL at Week 1 to 68 mcg/dL at Week 7. The decrease of zinc concentration over the 7-week study period was greatest in the 40 mcg/kg/day group, followed by 100, 200, and 400 mcg/kg/day group. At Week 7, mean serum zinc concentrations remained within the normal range in the 200 and 400 mcg/kg/day dose groups, whereas mean zinc concentrations were below 60 mcg/dL at Week 6 and Week 7 in the 40 and 100 mcg/kg/day groups, respectively. These results supported the 400 mcg/kg/day dose for preterm neonates receiving PN and indicated that the 40 mcg/kg/day dose was inadequate.

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

The recommended dosing regimens are appropriate for general adult and pediatric populations receiving Zinc Sulfate Injection as a source of zinc for PN when oral or enteral nutrition is not possible, insufficient, or contraindicated. Of note, the dosage should be further individualized based on the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral zinc intake.

The general dosage recommendation of 3 mg/day for adults is supported by the results from a randomized controlled study that evaluated 24 patients with gastrointestinal disease requiring PN (3). Patients were randomized to receive low dose (0, 1.5, and 3 mg) or high dose (6, 12, and 23 mg) of zinc supplementation during a 3-week study period. The order of the three doses of zinc supplementation within each dose group was randomized so that zinc supplementation in the previous week would not affect the subsequent week in a consistent manner. Regression analysis showed a positive correlation between the amount of zinc lost from the GI tract and the weight of the GI contents lost or excreted ($p < 0.001$). In patients who did not lose >300 g/day of stool and/or small intestinal drainage, zinc balance was achieved with 3 mg/day of supplemental zinc. In the remaining patients, zinc losses were dependent upon the volume of GI fluid lost and the presence or absence of high urinary nitrogen losses and additional zinc replacement was needed. Regression analysis estimated that for patients with small bowel fluid lost, an additional zinc of 12.2 mg per each liter of small bowel fluid lost is needed. For patients with ileostomy, an additional zinc of 17.1 mg per each kg of stool or ileostomy output is needed.

The general recommended dose of 400 mcg/kg/day for preterm neonates <3 kg is supported by the study results from Lockitch G et al. as described above (10, 94). Please see Section 10 for information regarding dosing recommendations for pediatric patients.

In conclusion, the recommended dosing regimens are summarized as below:

For metabolically stable adult patients, the recommended daily dosage is a 3 mg/day of elemental zinc, with a potential need for a higher daily dosage in monitored patients with small bowel fluid loss or excess stool or ileostomy output.

The recommended pediatric dosage is shown in Table 1 by age and estimated weight. The dosages in the table are general recommendations intended for most pediatric patients. However, based on clinical requirements, some patients may require a higher dosage.

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

No alternative dosing regimen or management strategy is required for subpopulations. The recommended dosing regimen is individualized based on the patient's age and body weight as well as clinical condition, nutritional requirements, and the contribution of oral or enteral zinc intake. The overall management strategy for all subjects receiving Zinc Sulfate Injection is described below.

Because plasma/serum zinc concentrations do not always accurately reflect total body zinc and signs and symptoms of zinc deficiency are non-specific, zinc concentrations and signs and symptoms of zinc deficiency should be monitored in patients during treatment, especially in pediatric patients. It is important to note that zinc concentrations may vary depending on the assay used and the laboratory reference range. More than 75% of whole blood zinc is present in erythrocytes; therefore, zinc concentrations in hemolyzed samples are falsely elevated due to release of zinc from the erythrocytes. The lower end of the reported range in healthy adults in plasma/serum is 60 mcg/dL. Observation of such a low zinc concentration during treatment warrants close monitoring of patients for signs and symptoms of zinc deficiency.
Zinc has a ubiquitous subcellular distribution and is involved in many biological processes. Therefore, clinical features of zinc deficiency are oftentimes non-specific. Deficiency may present in the form of skin disorders, diarrhea, short stature with impaired development, hypogonadism, cognitive dysfunction, anorexia, impaired taste and smell, altered wound healing, and bacterial infections (95). Acrodermatitis enteropathica is a rare inherited form of zinc deficiency consisting of scaly, red, desquamating lesions involving the nasolabial folds and hands. In severe cases it extends to the trunk, resulting in extensive exfoliation and secondary skin infection. There is often loss of hair (1).

Plasma/serum zinc concentrations are commonly used for monitoring patients on PN. However, monitoring of zinc deficiency using laboratory values alone can be difficult because plasma/serum zinc concentration does not always accurately reflect total body zinc, and circulating zinc is rapidly turned over to meet tissue requirements. In addition, zinc concentrations may vary depending on the assay used and the laboratory reference range. Blood collection, processing, and storage before sample analysis can also impact the accuracy of the analysis. For instance, zinc concentrations in hemolyzed samples are falsely elevated due to release of zinc from the erythrocytes, as more than 75% of whole blood zinc is present in erythrocytes (77). Different zinc concentrations have also been found in samples collected with different collection tubes and anticoagulants (77), and rubber stopper and clot activator contributed to zinc contaminants (96). Therefore, collection of blood for analysis of zinc concentrations should be performed using collection tubes specially designed to be zinc-free.

The collection, processing, and storage of blood samples for zinc analysis should be performed according to the laboratory's sample requirements. According to the reference range from three different reference laboratories (Table 3), the lower limit of the reference range in adults is 60 mcg/dL.

Taken together, zinc concentrations and sign and symptoms of zinc deficiency should be monitored in patients during treatment, especially in pediatrics. Close monitoring of patients for signs and symptoms of zinc deficiency during treatment is warranted when zinc concentrations are at the lower end of the reported range.

Table 3: Reference Range for Zinc Concentration in Three Reference Laboratories

Laboratory	Sample Type	Reference Range	
LabCorp	Plasma/serum	56 – 134 mcg/dL	
Quest Diagnostics	Plasma/serum	≤5 Months	26-141 mcg/dL
		6-11 Months	29-131 mcg/dL
		12-23 Months	31-120 mcg/dL
		2-3 Years	29-115 mcg/dL
		4-5 Years	48-119 mcg/dL
		6-9 Years	48-129 mcg/dL
		10-13 Years	25-148 mcg/dL
		14-17 Years	46-130 mcg/dL
		Adult	60-130 mcg/dL
Mayo Clinic Laboratories	Serum	0-10 years	60-120 mcg/dL
		> or =11 years	66-110 mcg/dL

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

There is a potential for drug-drug interaction between intravenous zinc and copper hemostasis. Subjects receiving prolonged treatment of PN supplemented with zinc should be monitored for signs and symptoms of copper deficiency. If a patient develops signs and symptoms of copper deficiency during treatment with Zinc Sulfate Injection, interrupt treatment with Zinc Sulfate Injection and check zinc, copper, and ceruloplasmin levels. Copper deficiency should be treated with supplemental copper administration and discontinuation of zinc supplementation.

Most of the drug-drug interactions of zinc involve changes in the absorption of the perpetrator or the victim drug when zinc is given by oral administration. For instance, large amounts of supplemental iron might decrease zinc absorption (97), and high zinc intake can inhibit copper absorption causing copper deficiency-associated anemia and myelopathy (98-101). Additionally, co-administration of oral zinc has been reported to decrease the absorption and exposure of tetracycline (102), ciprofloxin (103), and cephalexin (104) and urinary excretion of norfloxacin (105). Concomitant zinc supplementation also decreased the concentrations of atazanavir and ritonavir (106) in human immunodeficient virus-infected subjects.

The modulation of metallothionein (MT) expression is proposed to be the mechanism underlying the interaction between oral zinc and copper absorption and deficiency. MT is a family of proteins that have the capacity to bind both physiological (including zinc and copper) and xenobiotic heavy metals. Copper and zinc are absorbed in the stomach and proximal duodenum and enter the enterocytes, where copper could be bound by MT or be free. Free copper can be transported from the enterocytes to the circulation, whereas the MT-bound copper remains in the enterocyte and is lost in the feces with the epithelial desquamation. Oral zinc therapy leads to elevated plasma/serum zinc concentration, which is believed to cause an up-regulation of MT synthesis in the enterocytes. Copper displaces zinc because of its higher affinity for MT and is sloughed off the intestinal tract leading to hypocupremia. Consistent with this hypothesis, increased MT concentrations in the duodenum have been found in Wilson's disease patients treated with oral zinc therapy (107).

Two cases of copper deficiency myelopathy secondary to parenteral zinc supplementation during chronic dialysis have been reported in the literature (108, 109). Both cases involved two elderly women (61 and 65 years old) who underwent dialysis with 100 to 150 mg zinc added to the hemodialysis solution. The patients experienced megaloblastic anemia and signs and symptoms of myelopathy. Laboratory findings revealed elevated zinc concentrations and low copper and ceruloplasmin concentrations. Zinc substitution during hemodialysis was discontinued and copper supplementation was initiated. In one of the patients, the symptoms were improved and copper and zinc concentrations resumed back to normal levels after 7 months of oral copper supplementation. The other patient recovered over a short time with few sequelae after IV copper supplementation. These findings support the notion that high plasma/serum zinc levels, in these two cases presumably caused by entry of zinc from the dialysate solution into the systemic circulation, could result in copper deficiency and associated symptoms. Based on these observations, the possibility of copper deficiency associated with intravenous zinc supplementation cannot be ruled out. Therefore, patients requiring prolonged treatment with PN supplemented with zinc should be monitored for signs and symptoms of copper deficiency. If a patient develops signs and symptoms of copper deficiency during treatment with Zinc Sulfate Injection, zinc treatment should be interrupted and zinc, copper, and ceruloplasmin levels be checked. Copper deficiency should be treated with supplemental copper administration and discontinuation of zinc supplementation.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

No clinical trial or study was conducted by the Applicant. This is an NDA application seeking a 505(b)(2) literature-only regulatory approval.

The Applicant submitted two types of articles:

- ASPEN clinical guidelines and
- Systematic Literature Review of zinc clinical studies by (b) (4)

The most relevant studies are summarized in the table below.

Table 4: Listing of the Most Pertinent Studies

	First Author, Year, Location	Patient Population Number of Patients Females/Males Age	Trace Element Administration	Reported Efficacy/Pharmacokinetic Findings
1	Wolman 1979 Canada (3)	Patients who required TPN for at least 3 weeks • N=24 • 10F/14M • Age Range: 16 to 70 years	Patients received: • Low Dose: Zinc 0, 1.5, and 3.0 mg/day for 1 week each, in random order (17 patients) • High Dose: Zinc 6, 12, and 23 mg/day for 1 week each, in random order (7 patients) The following trace elements were also added to the TPN: copper 1.6 mg, manganese 0.8 mg, and selenium 120 µg.	• Plasma zinc rose with increasing daily intake of zinc. • Overall, zinc balance was almost achieved in patients receiving zinc 6 mg/day and a positive balance was achieved in patients receiving zinc 12 mg/day. • Excluding patients with significant diarrhea, positive zinc balance was achieved with zinc 3 mg/day in all but 1 patient.
2	Ricour 1977 (5)	Eight infants and two children (age 2 and 8 years)	Doses of zinc: • 0.03 mg/kg/day (n=5) • 0.05 mg/kg/day (n=5)	• Neither the 0.03 mg/kg/day nor the 0.05 mg/kg/day dose prevented zinc depletion in plasma.
3	Dahlstrom 1986 (US, Sweden) (6)	Patients aged 4 to 65 months receiving PN N=19 patients Sex:7F/12M Mean age: • 31.6 months in group 1 • 33.6 months in group 2	Patients were divided into 2 groups: • Group 1: ingested 0 to 10% of their daily energy requirements enterally; majority of nutrition was PN (9 patients) • Group 2: ingested 30 to 70% of their daily	• The mean serum zinc concentration in group 1 was higher than in controls. • The mean serum zinc concentration in group 2 was similar to controls. • There were no obvious clinical signs or symptoms of zinc deficiency.

	First Author, Year, Location	Patient Population Number of Patients Females/Males Age	Trace Element Administration	Reported Efficacy/Pharmacokinetic Findings
		Controls were age- and sex-matched.	energy requirements enterally; minority of nutrition was PN (10 patients) Control: healthy children not receiving PN with the same age and sex distribution (19 patients) Zinc 2 mg/L and copper 1 mg/L were added to PN in groups 1 and 2. Groups 1 and 2 had received PN for a mean of 28.4 and 23.1 months, respectively.	• An adequate dosage of zinc was reported as 2 mg/L, but it is not clear from the publication the volume of TPN patients were receiving per day. The authors state the dosage needed to prevent clinical and biochemical deficiency was consistent with that reported by Lowry in 1981.
4	Lowry 1981 US (4)	Tumor-bearing patients receiving TPN N=24 Sex not reported Age Range: 10 to 69 years	Patients received a trace element supplement with TPN (20 patients) for a mean duration of 22 days. The trace element supplement (approximately 2.0 mL/day) provided zinc 2.0 mg/mL, copper 1.4 mg/mL, and manganese 0.2 mg/mL. Control patients did not receive a trace element supplement with TPN (4 patients).	• Patients with trace element supplementation maintained serum zinc and copper within the reference range, as compared to progressive decline of concentrations in the control group. • A daily dosage of 70 to 80 mcg/kg/day of zinc was found to maintain normal blood concentrations.
5	Zlotkin 1983 Canada (7)	15 premature (mean weight 1.2 kg; mean of 28 weeks GA), 8 full-term small for gestational age (2.3 kg; 38 weeks GA) and 15 full term infants (3.2 kg; 39 weeks GA).	For 6 days patients received 3 dosage levels (low dosage corresponding to zinc in human breast milk; middle dosage to AMA recommendations; and high dosage approximating in utero accretion rate).	• The authors concluded that in order to prevent zinc deficiency in preterm infants, larger quantities of zinc must be provided to replace ongoing losses and build up body stores (to meet the needs of rapid protein synthesis and prevent growth impairment). • The authors concluded that 438 mcg/kg/day is required in pre-term infants; whereas, in full-term small for gestational age and full-term infants a dosage of above 150 mcg/kg/day is adequate.

	First Author, Year, Location	Patient Population Number of Patients Females/Males Age	Trace Element Administration	Reported Efficacy/Pharmacokinetic Findings
6	Suita 1984 Japan (8)	premature and full-term infants	zinc-supplemented PN for 4 weeks	• A dosage of 40 mcg/kg/day was sufficient in full-term infants but was an inadequate dosage for premature infants.
7	James 1976 Australia (9)	premature infants (less than 1.05 kg)	balance study over 3 to 4 weeks	• recommended a dosage of 200 mcg/kg/day.
8	Lockitch 1985 Canada (10) and Lockitch 1983 Canada (94) Note: this study appears to have been also published in 1983.	Low birthweight (<2000 g) infants who commenced PN during the first 10 days of life N=105 Sex not reported. Age not reported.	Patients were randomized to receive: • Group 1: zinc 0.04 mg/kg/day + copper 0.02 mg/kg/day • Group 2: zinc 0.10 mg/kg/day + copper 0.02 mg/kg/day • Group 3: zinc 0.10 mg/kg/day + copper 0.04 mg/kg/day • Group 4: zinc 0.20 mg/kg/day + copper 0.02 mg/kg/day • Group 5: zinc 0.20 mg/kg/day + copper 0.04 mg/kg/day • Group 6: zinc 0.40 mg/kg/day + copper 0.02 mg/kg/day • Group 7: zinc 0.40 mg/kg/day + copper 0.04 mg/kg/day Supplements were added to Pediatric Electrolyte Solution and infused with the first 12-hour infusion fluids each day from mid-afternoon to early the following morning. Article has insufficient information to calculate number of patients per group.	• There was a decline in mean serum zinc concentration of 46 mcg/dL over 7 weeks for the group as a whole. • The drop in serum zinc levels was greater in the lowest zinc supplement group than in the higher groups. • No change in mean zinc concentration was seen over 2 weeks in the highest supplement group. • By Week 6, a drop in mean concentration of 33 mcg/dL had occurred. However, the mean value remained within the normal range even at Week 7 in this group.

	First Author, Year, Location	Patient Population Number of Patients Females/Males Age	Trace Element Administration	Reported Efficacy/Pharmacokinetic Findings
9	Friel 1984 Canada (11)	22 preterm infants (mean weight of 0.9 kg and 27.5 weeks gestation)	PN supplemented with 350 mcg/kg/day	• found this dosage maintained serum zinc concentrations
10	Huston 1991 United States (110) Note: Article states TPN although patients were also receiving enteral feedings.	Premature low birthweight (<1000 g) infants without evidence of congenital metabolic or chronic white blood cell disease N=20 Sex not reported Mean gestational age: • 26.7 weeks selenium • 26.5 weeks control	Patients were randomized to receive: • Selenium Group: TPN including zinc 0.3 mg/kg/day, copper 0.02 mg/kg/day, and manganese, supplemented with selenium (as selenious acid) 1.5 mcg/kg/day (10 patients); • Control Group: TPN including zinc 0.3 mg/kg/day, copper 0.02 mg/kg/day, and manganese (10 patients) Administered until full oral feeding volumes were attained.	• No significant changes in zinc or superoxide dismutase were observed in either group. • Although both groups received copper, serum copper concentrations declined significantly in the selenium group at the time enteral feedings were initiated, whereas no significant changes were observed in the control group. • Selenium concentrations declined to equally low levels in both groups when TPN was discontinued, but were significantly higher in the selenium group at the time enteral feedings were initiated. • Glutathione peroxidase activities significantly increased in the selenium group at the time enteral feedings were initiated, then tended to decrease. In the control group, glutathione peroxidase tended to increase, then decreased significantly when TPN was discontinued.

7.2. Review Strategy

No clinical trials were conducted by the Applicant in support of this submission. However, the Applicant commissioned the (b) (4) ((b) (4) to conduct a systematic literature review (SLR) to provide data supporting efficacy and safety of parenteral zinc. The protocol-based SLR of parenteral use of zinc in adults and pediatric populations was designed and reported in conformance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (111). Additionally, a SLR on the oral and enteral use of TEs was performed to supplement the parenteral route evidence. In the format of the framework requested by the Division, a tabular summary of the published literature was submitted to

support the efficacy and safety of parenteral zinc in adult and pediatric populations for the proposed indication.

(b) (4) identified 69 publications reporting on zinc exposure in adults and 31 in pediatric populations, including randomized, placebo- and active-controlled clinical trials in a range of patient populations (neonatal, pediatric, and adult), that primarily evaluate the effect of intravenous zinc supplementation in patients on chronic PN. An additional 34 publications not captured by (b) (4) based on an independent assessment of the SLR was identified during the NDA review. The published studies are variable in study design, data collection/analysis, dosing, and efficacy and safety assessments; however, the time and extent of parenteral zinc use in clinical practice for supplementation purposes was taken into consideration.

The clinical review was based on the publications described above. The review strategy focused on the assessment of the evidence of the publications. In addition, the clinical review evaluated the clinical data that were the basis of the ASPEN guidelines.

8 Clinical Evaluation

8.1. Review of Efficacy

8.1.1. Assessment of Zinc Concentrations

Assays to measure serum and plasma zinc concentrations are the most widely available assays in clinical practice and are most often reported in the assessment of zinc deficiency. Zinc concentrations may vary depending on the assay used and the laboratory reference range; zinc concentrations in hemolyzed samples are elevated due to release of zinc from the erythrocytes [see Section 6 (Clinical Pharmacology) of this Multidisciplinary Review].

Several studies have tried to assess zinc concentrations in healthy subjects to establish a reference standard (112). See further discussion of laboratory reference ranges in Section 6 (Clinical Pharmacology) of this Multidisciplinary Review. Similar to the adult laboratory reference ranges for zinc for LabCorp, Quest Diagnostics, and Mayo Clinic Laboratories (56 to 134 mcg/dL, 60 to 130 mcg/dL, and 66 to 110 mcg/dL, respectively)(see Section 6 (Clinical Pharmacology) of this Multidisciplinary Review), the adult laboratory reference range for zinc in published studies enrolling a North American population was reported as 55 to 150 mcg/dL (113, 114) and 60 to 130 mcg/dL (115).

The Applicant provided literature reports assessing zinc levels achieved after intravenous administration of various doses of zinc, including doses lower and higher than the Applicant's proposed dosage. Based on the benefit of maintenance of normal zinc concentrations, it may be concluded that low zinc concentrations lead to adverse clinical outcomes, such that maintaining a normal zinc concentration and/or restoring zinc to normal concentrations in these studies is sufficient to accept measurement of zinc concentrations as a surrogate efficacy endpoint.

Although studies have not shown a consistent correlation between low zinc concentrations and onset/development of clinical deficiency or severity of clinical symptoms, patients can be appropriately monitored for efficacy using a combination of both serum concentrations and clinical signs and symptoms.

8.1.2. Evolution of Studies Evaluating Parenteral Zinc Supplementation

Zinc was not recognized as an essential trace element until 1984, when it was recommended as an additive to PN by the American Medical Association (31). Literature in the 1970s and 1980s described case reports, descriptive studies evaluating zinc supplementation in PN, and non-randomized studies of outcomes in patients on PN containing variable amounts of zinc (see Section 2.1.2 (Zinc) of this Multidisciplinary Review). However, it is important to note that not all patients with plasma zinc levels below the reference range developed clinical symptoms. Also, zinc supplementation in PN and monitoring of zinc levels were not standard practices

during that time, and therefore, such patients who were on long-term PN were likely to develop zinc deficiency as described in the literature. Since then, there has been increased awareness of the need to supplement patients, especially those on long-term PN who are at risk of developing zinc deficiency.

8.1.3. Review of Literature of Intravenous Zinc Sulfate Relevant to NDA

The publications used to support the use of parenteral zinc as a nutrient source in patients on PN are discussed in Sections 8.1.3.1 through 8.1.3.10 below.

8.1.3.1. Wolman et al. (1979) (Canada)(3)

Title:
Zinc in Total Parenteral Nutrition: Requirements and Metabolic Effects

Study Objective:
The purpose of this study was to determine the effect of varying doses of parenteral zinc (as zinc sulfate) on the zinc status of patients on TPN.

Study Design:
A randomized, dose-response, crossover study that evaluated (over three consecutive one-week periods) the effect of parenteral zinc (as zinc sulfate) on plasma zinc concentration.

Study Population:
Investigators in Toronto enrolled 24 stable TPN-dependent patients. Median age was 37 years and age ranged from 16 to 70 years. Median body weight was 55.2 kg and weight ranged from 29.0 to 83.5 kg. The number of females and males was 10 and 14, respectively. The patients did not receive enteral nutrition.

Study Treatment and Duration:
Duration: 3 weeks total
Treatment: Patients on PN received supplemental zinc/day as follows:

- Group 1 (N=17); randomization during each study week to the following:
  - 0.0 mg
  - 1.5 mg
  - 3.0 mg
- Group 2 (N=7); randomization during each study week to the following:
  - 6.0 mg
  - 12.0 mg
  - 23.0 mg

It should be noted that Zinc natively present in TPN solutions provided an estimated zinc input of 1.0 mg/day.

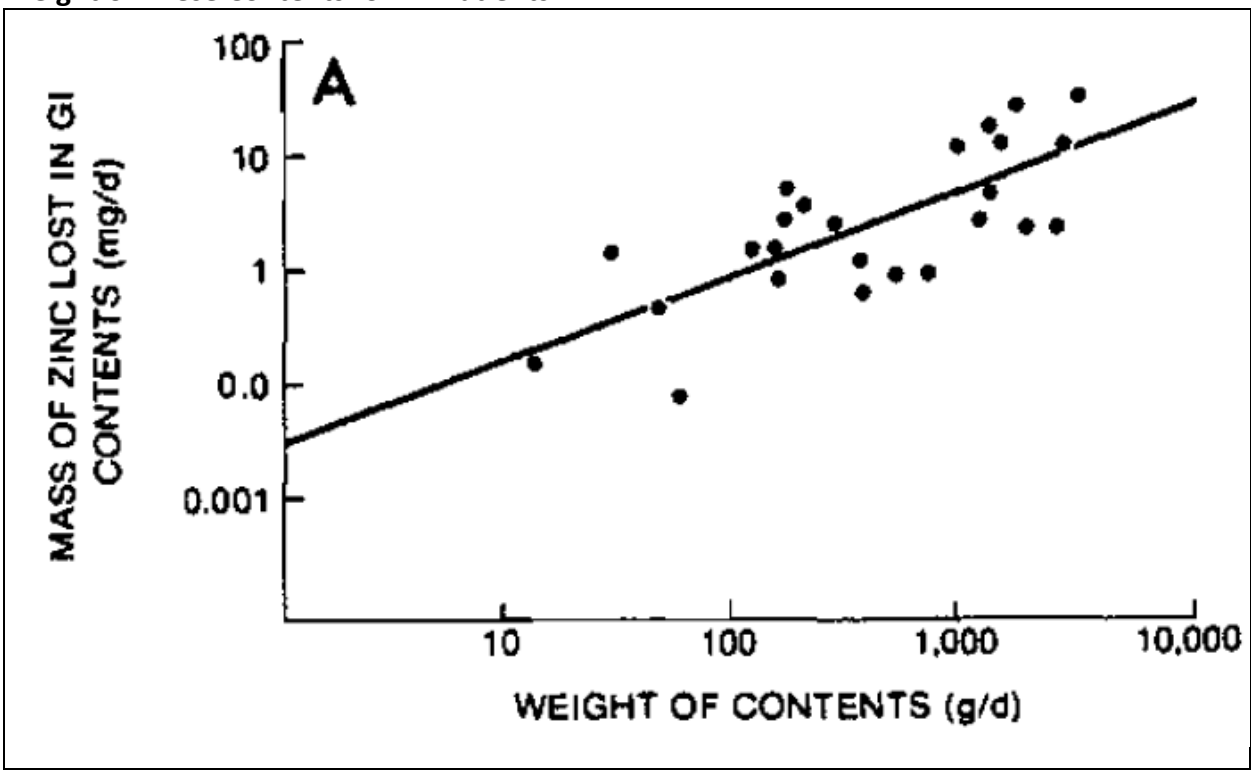
Assessments:

Blood samples were collected on Days 1, 3, and 7 of each study week. Collections of stool and urine were made for each 24-hour period of the study.

Results/Conclusions:

Regression analysis showed a positive correlation between the amount of zinc lost from the GI tract and the weight of the GI contents lost or excreted ($p < 0.001$). See the figure below.

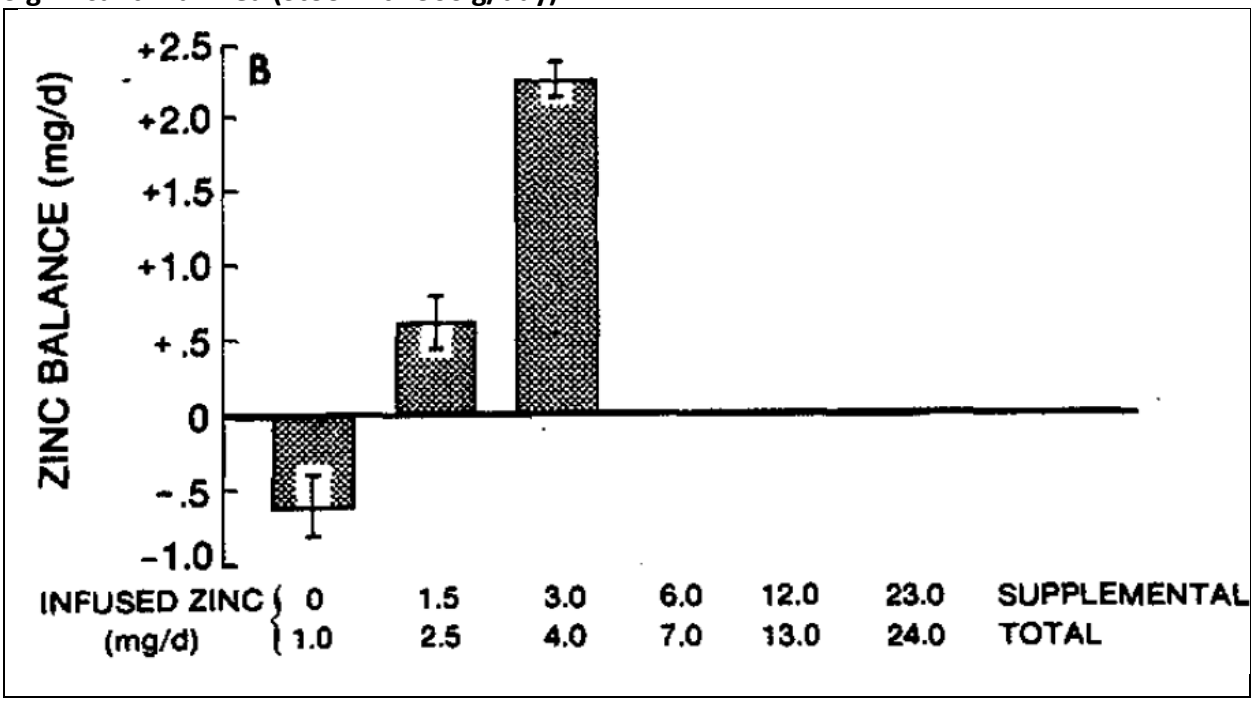
Figure 1: Log-Log Plot of Regression Analysis of Zinc Lost in Gastrointestinal Contents vs. Weight of These Contents for All Patients



Note: Each point represents the mean of a 3-week study ($P < 0.001$)

In patients who did not lose >300 g/day of stool and/or small intestinal drainage, zinc balance was achieved with 3 mg/day of supplemental zinc. See the figure below.

Figure 2: Zinc Balance in Relation to the Amount of Zinc Infused in Nine Patients Without Significant Diarrhea (Stool wt <300 g/day)



Note: All plasma zinc values were corrected by a factor of 10% for the zinc content of blank tubes.

In the remaining patients, zinc losses were dependent upon the volume of GI fluid lost and the presence or absence of high urinary nitrogen losses and additional zinc replacement was needed. Regression analysis estimated the following:

- For patients with small bowel fluid lost, an additional zinc of 12.2 mg per each liter of small bowel fluid lost is needed.
- For patients with ileostomy, an additional zinc of 17.1 mg per each kg of stool or ileostomy output is needed.

8.1.3.2. Ricour et al. (1977) (France) (5)

Title:
Estimates of trace elements requirements of children receiving total parenteral nutrition

Study Objective:
To estimate TE requirements of children on TPN

Study Design:
Dose-ranging study (two dose arms)

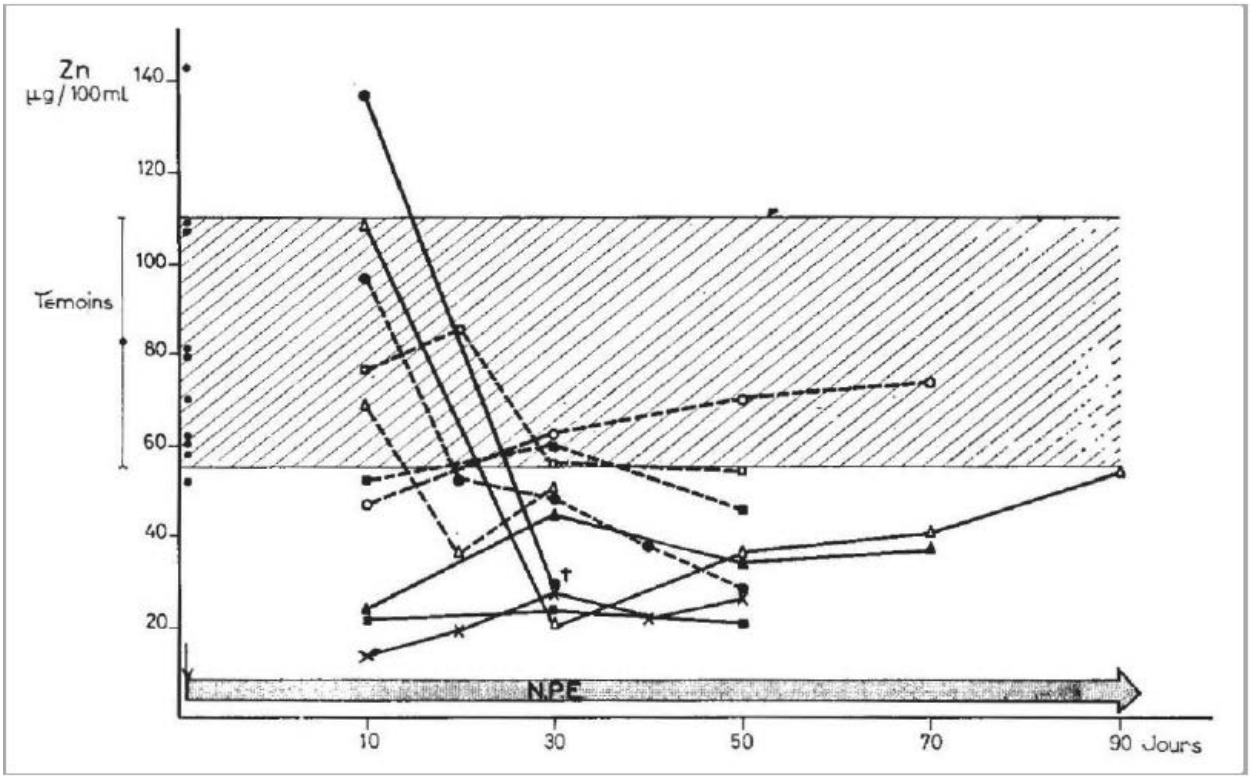
Study Population:
The study population consisted of eight infants and two children (age 2 and 8 years) starting PN.

Study Treatment and Duration:
Study treatment was 0.03 mg/kg/day (n=5) or 0.05 mg/kg/day (n=5). See study duration in the figure below.

Assessments:
Assessments included zinc concentrations in plasma.

Results/Conclusions:
Neither the 0.03 mg/kg/day nor the 0.05 mg/kg/day dose prevented zinc depletion in plasma. See the figure below.

Figure 3: Plasma Zinc Concentrations in 10 Pediatric Patients During Parenteral Nutrition Containing Zinc Dosed at 30 mcg/kg/day (Unbroken Line, N=5) or 50 mcg/kg/day (Broken Line; N=5)



Note: The hatched space identifies a normal range, as defined by 10 well-nourished children without digestive disease
The above figure is taken from the DEPI Review. Source is Figure 2 of Ricour 1977.

The authors concluded that daily intakes of zinc should be 100 mcg/kg/day.

8.1.3.3. Dahlstrom et al. (1986) (US, Sweden) (6)

Title:
Serum trace elements in children receiving long-term parenteral nutrition

Study Objective:
To determine whether there were any deficiencies of the trace elements in the serum and if the children had known or unrecognized signs or symptoms of trace element deficiency

Study Design:
Patients were divided into 2 groups and a healthy control group was included:

- Group 1: ingested 0 to 10% of their daily energy requirements enterally; the majority of nutrition was PN (nine patients)
- Group 2: ingested 30 to 70% of their daily energy requirements enterally; the minority of nutrition was PN (10 patients)
- Control: healthy children not receiving PN with the same age and sex distribution (19 patients)

Study Population:
Infants and older pediatric patients (aged 4 to 65 months).

Study Treatment and Duration:
Zinc 2 mg/L and copper 1 mg/L were added to PN in groups 1 and 2.

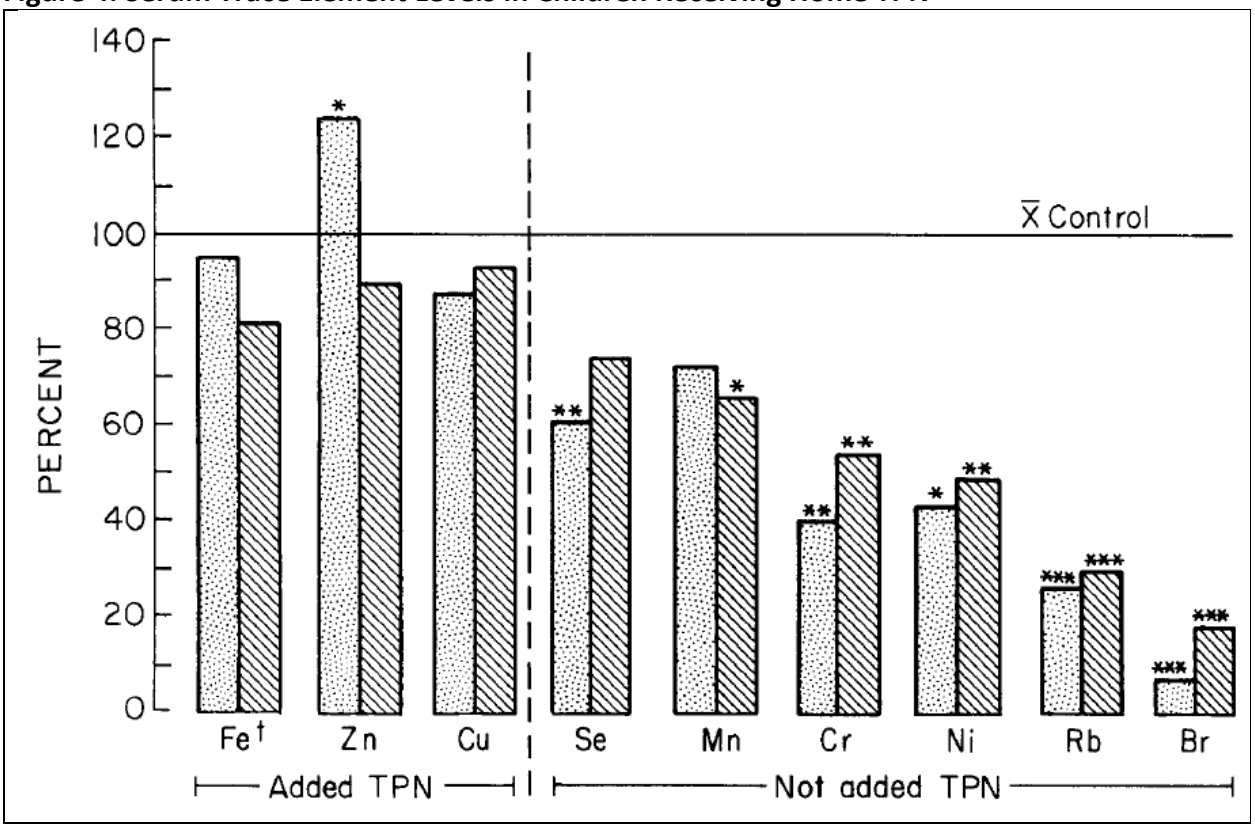
Note: It is not clear from the publication the volume of TPN that patients were receiving per day.

Long-term home PN (mean of approximately 2 years): Groups 1 and 2 had received PN for a mean of 28.4 and 23.1 months, respectively.

Assessments:
Assessments included zinc concentrations at the monthly visit to the TPN clinic.

Results/Conclusions:
The mean serum zinc concentration in Group 1 was higher than in controls. The mean serum zinc concentration in Group 2 was similar to controls. See the figure below.

Figure 4: Serum Trace Element Levels in Children Receiving Home TPN



Note: Patient values represent percentage of mean values for each trace element in healthy control children of same age range. Dotted and hatched bars represent group 1 and group 2 patients, respectively. Significantly different from 100% of normal mean values: *P <0.05, **P <0.01, ***P <0.001. †Fe added periodically to TPN solutions. There were no obvious clinical signs or symptoms of zinc deficiency.

An adequate dosage of zinc was reported as 2 mg/L, but it is not clear from the publication the volume of TPN patients were receiving per day. The authors state the dosage needed to prevent clinical and biochemical deficiency was consistent with that reported by Lowry in 1981.

8.1.3.4. Lowry et al. (1981) (US) (4)

Title:
Zinc and copper replacement during total parenteral nutrition

Study Objective:
To define an intake of zinc and copper that will prevent significant alterations of serum levels and provide consistently positive urinary retention of zinc and copper

Study Design:
Controlled study

- Patients received a trace element supplement with TPN (20 patients).
- Control patients did not receive a trace element supplement with TPN (four patients).

Study Population:
Tumor-bearing patients receiving TPN; N=24; Sex not reported; Age Range: 10 to 69 years

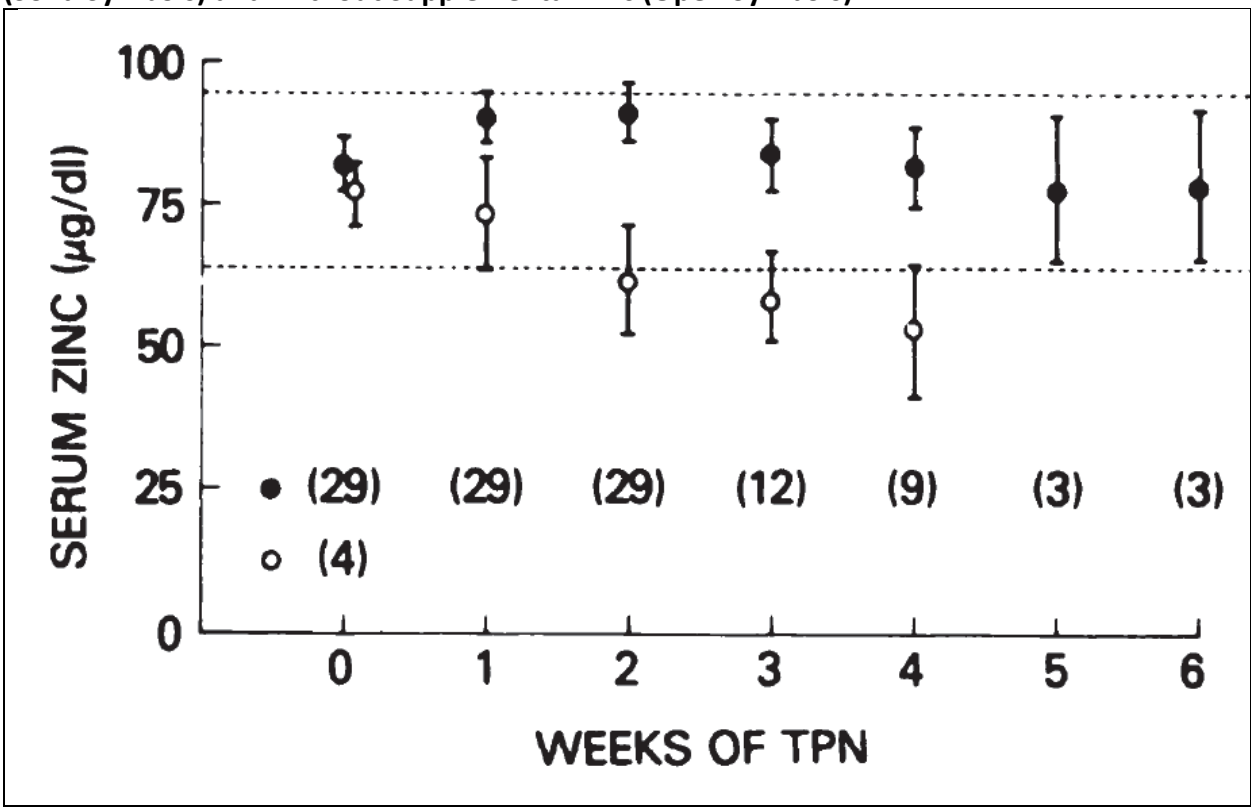
Study Treatment and Duration:
The trace element supplement (approximately 2.0 mL/day) provided zinc 2.0 mg/mL, copper 1.4 mg/mL, and manganese 0.2 mg/mL.

Mean duration of 22 days

Assessments:
Assessments included serum zinc levels before and during TPN.

Results/Conclusions:
Serum zinc during the first 2 weeks of TPN increased in patients supplemented with zinc and decreased in patients not supplemented with zinc (see the figure below).

Figure 5: Serum Zinc Concentrations, Mean ± Standard Error, During Episodes of TPN With (Solid Symbols) and Without Supplemental Zinc (Open Symbols)



Source: Figure 1 in Lowry 1981
Note: A daily dosage of 70 to 80 mcg/kg/day of zinc was found to maintain normal blood concentrations.

8.1.3.5. Zlotkin et al. (1983) (Canada) (7)

Title:
Meeting zinc and copper intake requirements in the parenterally fed preterm and full-term infant

Study Objective:
To determine the intravenous zinc and copper intakes required to build up body stores in the preterm infant and achieve positive retention in full-term infants

Study Design:
Random assignment of 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.

Study Population:
15 premature (mean weight 1.2 kg; mean of 28 weeks GA);
8 full-term small for gestational age (2.3 kg; 38 weeks GA) and
15 full term infants (3.2 kg; 39 weeks GA)

Study Treatment and Duration:
0.14 mg/kg/day (corresponding to zinc in human breast milk),
0.29 mg/kg/day (corresponding to AMA recommendations), or
0.49 mg/kg/day (approximating *in utero* accretion rate)

Duration of 6 days

Assessments:
Assessments included zinc measured in urine, stool, and nasogastric aspirate.

Results/Conclusions:
Full-term Infants: Estimated 0.15 mg/kg/day as the minimum zinc dose needed by infants to replace zinc normally lost in urine and stool. It should be noted that although infants were originally randomized into three zinc levels for each gestational age, the actual analysis of administered samples showed a wide range of values at each level; thus correlation analysis rather than group analysis was used.

Premature Infants: 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). It should be noted that zinc retention in utero of 0.24 mg/kg/day was described by the author based on a reference to another published article (Shaw JCL: Trace elements in the fetus and young infant. I. Zinc. Am J Dis Child 133:1260, 1979).

8.1.3.6. Suita et al. (1984)(Japan) (8)

Title:
Zinc and Copper Requirements During Parenteral Nutrition in the Newborn

Study Objective:
To determine zinc and copper intake requirements during PN in the newborn (pre-term infants and full-term infants)

Study Design:
Randomized controlled study

Study Population:
Post-surgical newborn infants (12 full term, 10 premature) were randomized to TPN with zinc 0.04 mg/kg/day added after either:

- Group 1: 4 weeks on TPN (N=10)
- Group 2: 1 week on TPN (N=12)

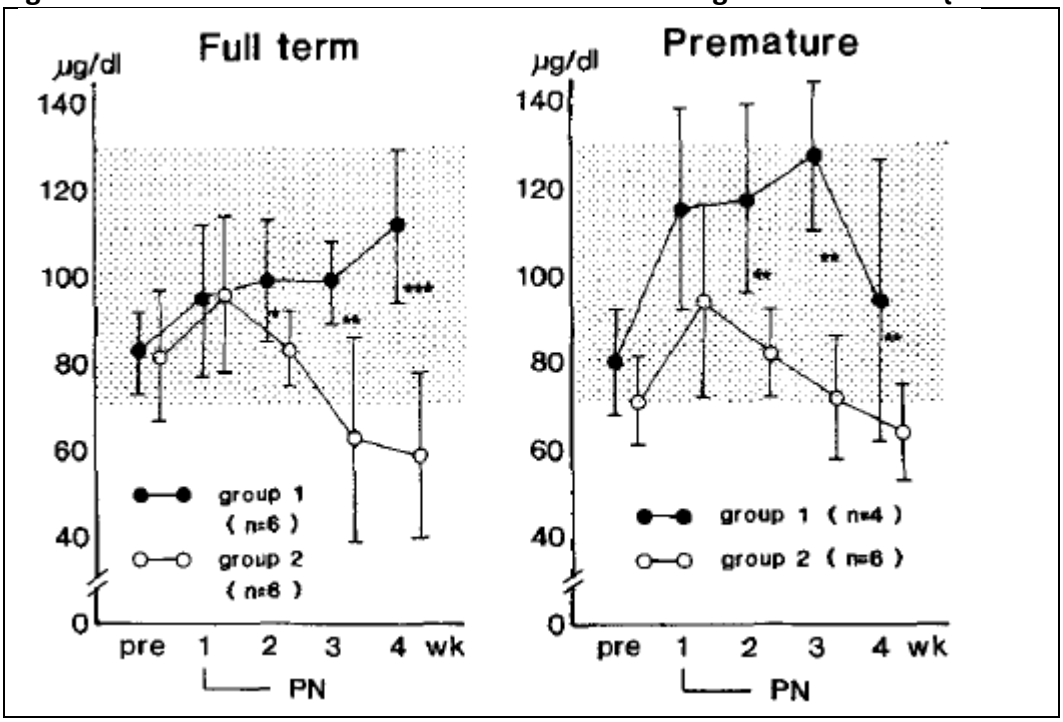
Study Treatment and Duration:
zinc 0.04 mg/kg/day

- Group 1: total duration of TPN, median 54.5 days, range 22 to 576 days
- Group 2: total duration of TPN, median 43.5 days, range 21 to 223 days

Assessments:
Assessments included zinc levels before and at weekly intervals during PN.

Results/Conclusions:
There was a progressive decline in zinc levels at the second week of PN in the non-supplemented group (Group 1) in both full term and premature babies and the rates were higher in the premature baby group. See the figure below.

Figure 6: Plasma Zinc Concentration Before and During PN for 4 weeks {Mean ± SD)



Note: *P <0.1 supplemented vs. unsupplemented group **P <0.05 ***P <0.01

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 4 weeks on zinc-supplemented TPN, some full-term infants had high serum zinc (up to 270 mcg/dL) without clinical evidence of toxicity. Thus, it was determined that a dosage of 40 mcg/kg/day was sufficient in full-term infants but was an inadequate dosage for premature infants or in infants losing intestinal fluids.

8.1.3.7. James et al. (1976)(Australia)(9)

Title:
Balance Studies of Nine Elements during Complete Intravenous Feeding of Small Premature Infants

Study Objective:
To assess the contribution of total intravenous nutrition in the care of the very small premature infant

Study Design:
Metabolic balance studies (determined amounts of 9 elements including zinc when given intravenously)

Study Population:
4 premature infants each weighing less than 1,050 g

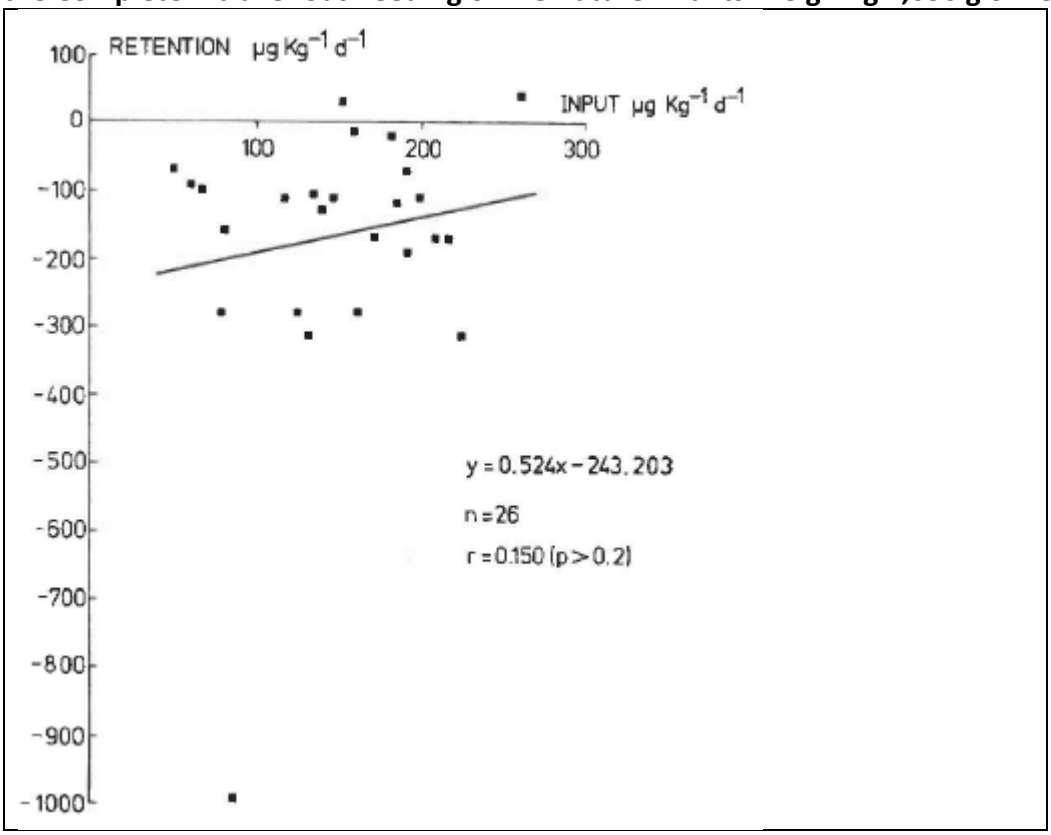
Study Treatment and Duration:
The IV input target of zinc for this study was 160 mcg/kg/day.

The duration was approximately 3-4 weeks (26 balance study periods each of 24 or 48 hours duration) during the complete IV feeding.

Assessments:
Assessments included urine samples tested for zinc concentrations, and limited serum samples tested for zinc concentrations.

Results/Conclusions:
The results obtained were extremely variable, all but two of the retention figures obtained being negative because of the very high concentrations of zinc in the urine of these infants. See the figure below.

Figure 7: Zinc-Regression Line of Input vs. Retention From 26 Balance Study Periods During the Complete Intravenous Feeding of Premature Infants Weighing 1,050 g or Less at Birth



The authors recommended a zinc dosage of 200 mcg/kg/day for this patient population.

8.1.3.8. Lockitch et al. (1985) (10) and Lockitch et al. (1983) (94) (Canada)

Title:
Serial changes in selected serum constituents in low birth weight infants on peripheral parenteral nutrition with different zinc and copper supplements

Study Objective:
To examine the effect of zinc and copper supplementation on serum zinc and copper concentrations and related biochemical values

Study Design:
Randomized dose-ranging study

Study Population:
127 premature infants (28 to 31 weeks of gestational age)

Study Treatment and Duration:
Patients were randomized to the following dose groups:

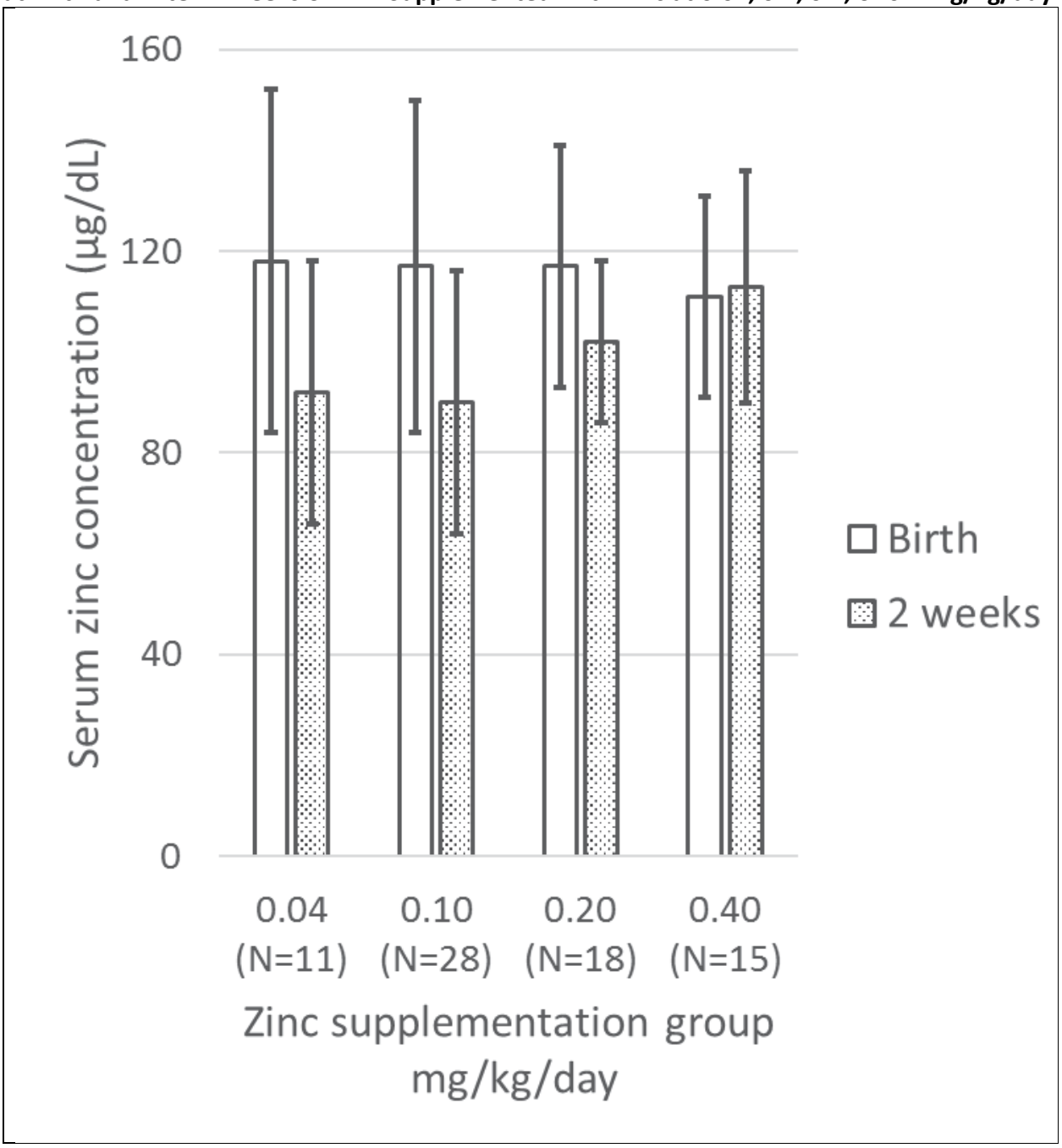
- Group 1: zinc 0.04 mg/kg/day + copper 0.02 mg/kg/day
- Group 2: zinc 0.1 mg/kg/day + copper 0.02 mg/kg/day
- Group 3: zinc 0.1 mg/kg/day + copper 0.04 mg/kg/day
- Group 4: zinc 0.2 mg/kg/day + copper 0.02 mg/kg/day
- Group 5: zinc 0.2 mg/kg/day + copper 0.04 mg/kg/day
- Group 6: zinc 0.4 mg/kg/day + copper 0.02 mg/kg/day
- Group 7: zinc 0.4 mg/kg/day + copper 0.04 mg/kg/day

Duration 2 weeks

Assessments:
Assessments included serum zinc concentrations before TPN commenced, and at 7 and 14 days after the initial specimen.

Results/Conclusions:
By the end of 2 weeks, only the zinc 400 mcg/kg/day group was able to maintain serum zinc concentrations in these premature infants. See the figure below (taken from the Division of Epidemiology I (DEPI) Review).

Figure 8: Serum Zinc Concentrations (Mean ± Standard Deviation) in Low Birthweight Infants at Birth and After 2 Weeks of TPN Supplemented With Zinc at 0.04, 0.1, 0.2, or 0.4 mg/kg/day



Source: Plot prepared by DEPI from summary data in Lockitch 1983

8.1.3.9. Friel et al. (1984) (Canada) (11)

Title:
Serum zinc, copper, and selenium concentrations in preterm infants receiving enteral nutrition or parenteral nutrition supplemented with zinc and copper

Study Objective:
To determine trace element requirements in preterm infants receiving enteral or PN

Study Design:
Non-randomized, controlled study

Study Population:
15 enterally fed preterm infants not receiving trace element supplementation (mean weight of 1.3 kg and 29.4 weeks gestation) and 22 preterm infants receiving total or partial PN (mean weight of 0.9 kg and 27.5 weeks gestation)

Study Treatment and Duration:
(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 PN (N=22; mean birthweight 909 gm; mean duration of PN 3 weeks).

Assessments:
Assessments included serum zinc concentrations measured at birth and after approximately 4 weeks.

Results/Conclusions:
Over the first 4 weeks of life, mean serum zinc (approximately 130 mcg/dL at birth) decreased by 30 to 40% and 15 to 20% in enterally and parenterally fed infants, respectively. See the table below.

Table 5: Mean (Standard Deviation) Serum Zinc

Trace Element (units)	Day	Enteral Nutrition		Parenteral Nutrition	
		N	Mean (SD)	N	Mean (SD)
Zinc (µg/dL)	1	14	126 (33)[a]	20	138 (36)
	7	14	103 (31)	18	121 (22)
	14	12	88 (30)	19	118 (29)
	21	7	77 (20)[a]	10	127 (27)[a]
	28	5	87 (40)	5	113 (28)

Abbreviations: SD-standard deviation

The authors concluded that the dosage studied maintained serum zinc concentrations in this patient population.

8.1.3.10. Huston et al. (1991) (US) (110)

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

Study Objective:
To study the effect of selenium supplementation upon trace metal metabolism in low-birthweight preterm infants <1000 g birthweight

Study Design:
Randomized, controlled, parallel-group study

Study Population:
Low birth weight (<1000 g) infants with no major congenital metabolic or chronic white blood cell disease

Study Treatment and Duration:
Twenty patients were randomly assigned into 2 groups of 10 infants each:

- One group received selenium supplementation (1.5 mcg/kg/day) and
- The other group received no selenium supplementation in their TPN solution

The article states TPN, although patients were also receiving enteral feedings.

Zinc dosage was 0.30 mg/kg/day in both groups.

Administered until full oral feeding volumes were attained.

- Age before initiation of TPN (sample A) was 4 days (mean in each group)
- Age at the time of initiation of oral feeding (sample B) was 15 days (mean in control group) and 14 days (mean in selenium group)
- Age at the time full oral feeding volumes were attained (sample C) was 42 days (mean in each group)

Assessments:
Assessments included blood samples drawn:

- before initiation of TPN (sample A),
- at the time of initiation of oral feeding (sample B), and
- at the time full oral feeding volumes were attained (sample C).

Results/Conclusions:
A dosage of 270 to 280 mcg/kg/day of zinc in premature infants (<1 kg and 26 weeks gestational age) was associated with decreasing serum zinc concentrations. See the table below.

Table 6: Mean (± Standard Deviation) Serum Zinc Concentrations

	Serum Zinc Concentrations		
Group	Sample A	Sample B	Sample C
Selenium Group	150 ± 79	104 ± 11	95 ± 38
Control Group	133 ± 36	103 ± 26	117 ± 69

The authors concluded that 270 to 280 mcg/kg/day of zinc in this patient population was not sufficient.

8.1.4. Specific Populations

Pregnancy/Lactation:
Literature evidence for zinc requirements in pregnancy, while scant, suggests that pregnant women have an increased metabolic demand for trace elements, including zinc due to fetal needs. Zinc deficiency has been reported to be associated with adverse pregnancy outcomes including fetal loss, congenital malformations, intrauterine growth restriction, low birth weight, prolonged labor, and preterm or post-term deliveries. Because zinc is secreted in breast milk, lactating women needed higher doses of zinc for their average daily requirements.

GI Fluid Losses:
See Section 8.1.3.1 for a discussion of the Wolman et al. (3) publication. In patients who did not lose >300 g/day of stool and/or small intestinal drainage, zinc balance was achieved with 3 mg/day of supplemental zinc. In the remaining patients, zinc losses were dependent upon the volume of GI fluid lost and the presence or absence of high urinary nitrogen losses and additional zinc replacement was needed. Regression analysis estimated that for patients with small bowel fluid loss, an additional 12.2 mg of zinc per each liter of small bowel fluid loss would be needed. For patients with ileostomy, an additional 17.1 mg of zinc per each kg of stool or ileostomy output would be needed.

8.1.5. Integrated Assessment of Effectiveness

To assess the efficacy of Zinc Sulfate Injection, the Applicant needed to demonstrate that the product adequately provided a supply of zinc as part of a PN regimen. The Division finds the literature submitted by the Applicant to be adequate and in general alignment with the approach previously agreed upon prior to NDA submission.

The published studies include metabolic balance studies and controlled clinical studies with limited efficacy and safety assessments. The time and extent of parenteral zinc use in adults and pediatrics in clinical practice for PN supplementation purposes also supports the proposed use.

The clinical trials used in the assessment of effectiveness have primarily focused on measurement of zinc levels before and after intravenous supplementation of zinc in PN and

have not routinely included clinical outcome assessments. However, establishing efficacy in clinical trials is not necessary to support the indication the Applicant seeks. The indication for Zinc Sulfate Injection as a source of zinc for PN is appropriate because an increase and/or maintenance of serum or plasma zinc concentrations in patients administered PN containing zinc sulfate has been demonstrated across multiple studies. Measurement of zinc levels before and after supplementation can be considered reasonably objective endpoints and therefore can distinguish the effect of zinc supplementation from spontaneous change due to the known natural course of a disease, a placebo effect or biased observations.

A study of the effects of doses of between 0 and 12 mg/day of parenteral zinc in adults for 3 weeks (3) found a positive correlation between the amount of zinc lost from the GI tract and the weight of the GI contents lost or excreted. In patients who did not lose >300 g/day of stool and/or small intestinal drainage, zinc balance was achieved with 3 mg/day of supplemental zinc. In patients with small bowel fluid loss and ileostomy, the amount of additional zinc needed was determined based on a regression analysis.

A study in eight infants and two children 2 and 8 years of age that studied the effect of zinc 30 or 50 mcg/kg/day in PN for approximately 4 weeks (5) concluded that higher doses (100 mcg/kg/day) are needed in this population. A study of infants/children 4 to 65 months of age given zinc 2 mg/L in PN for a mean duration of approximately 2 years (Dahlstrom et al. 1986) concluded that 70 to 80 mcg/kg/day was appropriate in this population. A study of patients 10 to 69 years of age receiving TE supplementation including zinc 2 mg/L vs. a control group not receiving TE supplementation (4) concluded that zinc 70 to 80 mcg/kg/day was appropriate in this population. A study that randomized premature, full term SGA, and full term infants to 6 days of 140 mcg/kg/day, 290 mcg/kg/day, and 490 mcg/kg/day (7) concluded that 438 mcg/kg/day is required in pre-term infants, whereas, in full-term small for gestational age and full-term infants a dosage of above 150 mcg/kg/day is adequate. A study that randomized premature and full term infants to TPN supplemented with zinc 40 mcg/kg/day for 4 weeks after either 1 week on TPN or 4 weeks on TPN (8) concluded that 40 mcg/kg/day is sufficient in full term infants but not in premature infants or infants losing intestinal fluids. A metabolic balance study in premature infants weighing less than 1050 grams with an IV input target of zinc 160 mcg/kg/day in TPN over approximately 3-4 weeks (9) concluded that a higher zinc dosage of 200 mcg/kg/day was appropriate in this population. A study that randomized premature infants 28 to 31 weeks of gestational age to zinc doses varying from 40 mcg/kg/day to 400 mcg/kg/day for 2 weeks (10) found that serum zinc concentrations were maintained only in the 400 mcg/kg/day group. A study of preterm infants with mean weight of 0.9 kg and 27.5 weeks gestation receiving either enteral feeding exclusively or PN with zinc 350 mcg/kg/day for 3-4 weeks (11) found that this dosage maintained serum zinc concentrations. A study of low birthweight preterm infants receiving zinc 270 to 280 mcg/kg/day until full oral feeding volumes obtained (110) concluded that this dose was insufficient as it lead to decreasing serum zinc concentrations.

Overall, the literature provides supportive evidence based on zinc levels for the use of intravenous zinc sulfate as a source of zinc to patients who cannot receive adequate nutrition through oral/enteral intake. These trials were evaluated in conjunction with the generally accepted scientific knowledge of the role of zinc in maintaining health and preventing/treating the potential clinical effects of deficiency. Studies and case summaries that assessed zinc-deficiency conditions demonstrated the role of zinc in treating these conditions, thereby supporting adequate daily intake of zinc in the service of preventing these conditions and providing it as a supplement in PN in those unable to take daily enteral feeds.

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

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

8.2. Review of Safety

8.2.1. Safety Review Approach

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

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

8.2.2. Review of the Safety Database

Overall Exposure

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

Adults

The Applicant submitted 69 publications reporting on 1550 adults exposed to parenteral zinc (age 18 to 87 years).

Four of these publications included safety information (Table 1 of Section Summary of Adult Clinical Safety, Module 2, Page 9/110). The dose and duration of zinc supplementation in the 4 studies with safety information are summarized below (see also the table below):

- Number of Patients: A total of 127 patients were exposed to zinc supplementation.
- Duration of Zinc Supplementation: The duration of zinc supplementation was ≤8 days in 3 of the 4 studies; duration was 64 weeks in the remaining study.
- Daily Doses: Daily doses of zinc ranged across studies from 3 mg to 30 mg.

Table 7: Zinc: Adult Dose and Duration of Supplementation

Author Year	Number of Patients Receiving Zinc	Daily Intravenous Dose of Zinc	Duration of Therapy
Braunschweig 1997(116)	21	30 mg	3 days
Berger 1998(117)	10 in trace element group	26 mg	8 days
	10 in control group	7 mg	8 days
Main 1982(118)	10	8 mg	64 weeks
Liu 2015(119)	76	3 mg	Mean of 5.2 days

Source: From NDA 209377 submission, Section Trace Element Injection (Adult), Module 2.7.4 Summary of Clinical Safety, Table 2, Page 13/110.

Pediatric Patients

The Applicant submitted 31 publications reporting on 549 pediatric patients on PN exposed to parenteral zinc (age newborn to 13 years).

Two of these publications included safety information (Table 4 of Section Summary of Pediatric Clinical Safety, Module 2, Page 14/66). The dose and duration of zinc supplementation in the 2 studies with safety information are summarized below (see also the table below):

- Number of Patients: A total of 30 patients were exposed to zinc supplementation.
- Duration of Zinc Supplementation: The duration of zinc supplementation ranged from 7 days to 3 weeks in the 2 studies.
- Daily Doses: Daily doses of zinc ranged from 0.04 mg/kg/day to 0.75 mg/kg/day.

Table 8: Zinc: Pediatric Dose and Duration of Supplementation

Author Year	Number of Patients Receiving Zinc	Daily Intravenous Dose of Zinc	Duration of Therapy
Pediatric			
Cvijanovich 2016(120)	6	0.25 mg/kg/day	7 days
	6	0.50 mg/kg/day	7 days
	6	0.75 mg/kg/day	7 days
Neonatal			
Suita 1984(8)	12	0.04 mg/kg/day	3 weeks

Source: From NDA 209377 submission, Section Trace Element Injection (Pediatric), Module 2.7.4 Summary of Clinical Safety, Table 4, Page 14/66.

Additional Literature (Adults and Pediatric *Patients)*
Additionally, DEPI identified 19 articles, from 17 studies, published before 2015, but not captured by (b) (4).

8.2.3. Safety Results

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

Adult Published Literature
Adverse events were not consistently reported in published literature. Diarrhea is the only adverse finding in the 4 adult safety parenteral zinc studies.

Pediatric Published Literature
Cvijanovich 2016 (120) was a non-randomized, controlled study of critically ill children aged 1 month to 10 years. All patients had at least one organ failure at the time of enrollment. Patients were sequentially enrolled into four dosing groups: (1) Control: No zinc (six patients); (2) Low dose: Zinc sulfate 0.25 mg/kg/day (six patients); (3) Medium dose: Zinc sulfate 0.5 mg/kg/day (six patients); and (4) High dose: Zinc sulfate 0.75 mg/kg/day (six patients). A total of 24 patients (including 6 controls) were enrolled. Median age ranged from 1.5 to 5.3 years across treatment groups and there were 14 females/10 males. One infant with respiratory syncytial virus sepsis developed refractory hypoxemia and required cannulation for extracorporeal membrane oxygenation on Day 6, but this event was reviewed by the Data Safety Monitoring Board and determined to be unrelated to the study.

Suita 1984 (8) was a randomized, controlled study of 22 full-term and premature infants who underwent major surgery and were placed on PN. The main indications for PN were short-bowel syndrome with enterostomy and bowel decompression for the infants with omphalocele or gastroschisis. Patients were randomized to one of two groups after surgery: (1) Group 1: No additional supplements (10 patients), or (2) Group 2: Zinc 0.04 mg/kg/day and copper 0.02 mg/kg/day after the 7th day of PN (12 patients). After 4 weeks of PN, infants in Group 1 who had to be left on PN were given supplements of zinc 0.04 mg/kg/day and copper 0.02 mg/kg/day. Mean duration of PN was 97 days, with a range of 21 to 576 days. Group 1 included six full-term and four premature infants. There were six females and four males. Birth weight ranged from 2700 to 3960 grams for full-term patients and from 1473 to 2450 grams for premature patients. Group 2 included six full term and six premature infants. There were five females and seven males. Birth weight ranged from 2580 to 3800 grams for full-term patients and from 1580 to 2490 grams for premature patients. In cases of PN over 4 weeks, full term infants with little loss of intestinal fluid had elevated plasma zinc levels over 150 to 270 mcg/dL while on a supplemental dose of 0.04 mg/kg/day. There were no clinical findings of zinc toxicity.

Additional Literature (Adults and Pediatric Patients)
The additional articles identified by DEPI did not provide new information regarding the safety of zinc for PN.

ASPEN recommends a dosage of 3 to 5 mg in adults (36). It is not clear what clinical data the guidelines rely on to support a dosage above 3 mg/day. However, the DEPI review, which summarizes the (b) (4) systematic review, describes several articles where dosages of 4 to 12 mg/day of zinc in PN were administered to adults without evidence of adverse reactions. See DEPI review for full citations:

- Messing 1977 [DEPI reference 71]. Included five patients receiving a mean 4.26 mg/day in PN.
- Lowry 1981 [reference 66]. Twenty cancer patients with 29 TPN episodes received supplemental zinc, approximately 4 mg/day, as zinc chloride.
- Main 1982 [DEPI reference 63]. 10 Crohn's disease patients before and after 14 episodes of TPN with trace metal solutions providing Zn 7.8 mg.
- Malone 1989 [DEPI reference 53]. 24 patients on long-term TPN (5 to 95 months) before and 1 to 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.
- Young 1996 [DEPI reference 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 to 12 mg/day; N=33).

In the study by Zlotkin et al. 1983 (7) enrolling premature and full term infants (see Section 8.1.3.5), doses of up to 824 mcg/kg/day were administered without evidence of adverse reactions.

8.2.4. Additional Safety Information

Human Carcinogenicity or Tumor Development
No reports linking parenteral zinc to carcinogenicity were identified in the literature.

Human Reproduction and Pregnancy
The Division of Pediatric and Maternal Health (DPMH) was consulted to assist with evaluating the safety of parenteral zinc in pregnancy and lactation. Refer to DPMH Maternal Health Labeling Review (Kristie Baisden, DO and Tamara Johnson, MD, MS) for additional details.

Briefly, published literature notes that pregnant and lactating women have an increased metabolic demand for trace elements, including zinc. Zinc deficiency is associated with adverse pregnancy outcomes including fetal loss, congenital malformations, intrauterine growth restriction, low birth weight, prolonged labor, and preterm or post-term deliveries.

DPMH determined that the Applicant conducted an adequate review of the published literature regarding zinc exposure during pregnancy and lactation. The available published literature is limited to oral zinc supplementation in pregnant and lactating women. Overall, the reports do not provide a clear association of adverse pregnancy outcomes associated with zinc use in pregnant women. DPMH agrees with the Applicant's conclusion that zinc supplementation appears to be safe in healthy pregnant and lactating women.

Pediatrics and Assessment of Effects on *Growth*

There are no adequate and well-controlled studies of zinc supplementation and effects on growth.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

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

There are reported cases of overdosage with intravenous zinc in PN:

- Faintuch et al. 1978 (121): Seven adult patients received an inadvertent overdosage of 50 mg to 75 mg elemental zinc per day in PN solution for 26 to 60 days; six of the seven patients developed hyperamylasemia (peak amylase values of 557 to 1850 Klein units; normal: 130 to 310). Amylase was not reported in one patient. Serum zinc concentrations ranged from 310 to 670 mcg/dL. None of the patients developed clinical signs of pancreatitis. Five of the seven patients died of septic complications.
- Brocks et al. 1977 (122): One adult patient died of infectious complications after receiving an inadvertent overdosage of 7.4 grams of zinc sulfate (equivalent to 1.2 grams of elemental zinc per day for 2.5 days) in PN solution over 60 hours. The serum zinc concentration was 4184 mcg/dL. Symptoms of zinc overdosage also included hyperamylasemia, thrombocytopenia, anemia, vomiting and diarrhea.
- Grissinger et al. 2011(123): One preterm infant born at 26 weeks gestation died of cardiac failure following a medication error in which the PN solution contained 330 mg/100 mL instead of 330 mcg/100 mL of zinc sulfate (overdosage of 1000-fold).

Safety Concerns Identified Through Post-Market Experience

The Division of Pharmacovigilance I (DPV-I) analyzed all adverse events associated with marketed unapproved Zinc Sulfate Injection or other zinc products in the FDA Adverse Event Reporting System (FAERS) database, the Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS), and Applicant's postmarketing surveillance databases, and reviewed the medical literature. A summary is presented below. Refer to the complete review by Drs. Jamie Ridley Klucken, Paolo Fanti, Lisa Harinstein, and Monica Muñoz for additional details.

The Applicant submitted 18 reports from their database containing adverse events suspected to be caused by exposure to parenteral zinc sulfate, Multitrace-4 (MTE-4) Concentrate, MTE-4 Pediatric, Multitrace-5 (MTE-5), or MTE-5 Concentrate. Of the 18 reports, 4 reported zinc

sulfate concentrate (i.e., marketed unapproved product) 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; one reported MTE-5 and MTE-5 concentrate as co-suspects. Based on review of the 18 adverse event reports, DPV-I concluded that none of the Applicant's reports were deemed possibly or probably related to intravenous zinc sulfate for the following reasons:

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

DPV-I additionally searched the FAERS database through May 1, 2019, CAERS database through May 5, 2019, and medical literature through May 31, 2019, and retrieved 4 FAERS cases, 3 CAERS cases, and 36 medical literature cases as discussed below.

The 4 FAERS cases involved intravenous (n=1) and oral (n=3) administration of zinc sulfate. The single case of intravenous zinc sulfate described 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 FAERS cases with oral zinc sulfate reported the adverse event of pancytopenia in association with copper deficiency (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.

The three CAERS cases involved oral zinc supplementation (salt formulation not specified); two reported hypersensitivity adverse events and one reported potential zinc toxicity without sufficient information for assessment. The cases do not inform the labeling of Zinc Sulfate Injection at this time due to the limitations of the cases and the products themselves (unregulated supplements which could contain other excipients or undeclared active ingredients).

The medical literature search yielded 30 cases describing medical complications known to occur in the context of excess zinc-induced copper deficiency after long-term use, including anemia, leukopenia, peripheral neuropathy. This analysis also found association of zinc-induced hypocupremia with six cases of nephrotic-range proteinuria. Notably, most cases of hypocupremia described the use of oral zinc products (16/30), but two cases were related to chronic systemic administration of an unspecified zinc salt 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.

The literature search also identified four cases of hypersensitivity reactions with zinc-containing insulin products, which resolved after switching to zinc-free insulin or after administering a reduced amount of zinc. In three of the four cases, additional testing confirmed 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.

Lastly, the literature search identified two cases of seizure that provided insufficient evidence to support labeling at this time; one case was deemed possible, although other etiologies could not be ruled out, and the other case was unassessable.

In conclusion, analysis of multiple postmarketing 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, DPV-I 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.

Expectations on Safety in the Post-Market Setting

There is substantial post-marketing experience in both adult and pediatric populations as well as patients with a broad range of underlying conditions (e.g., burns, post-surgery, critical illness, chronic malnutrition) based on the marketed, unapproved intravenous zinc sulfate alone or as a component in MTE-4 Concentrate, MTE-4 Pediatric, MTE-5, or MTE-5 Concentrate.

The recommended adult and pediatric age and body-weight adjusted dosage for Zinc Sulfate is below the UL for oral zinc. Therefore, it is unlikely that new safety information will arise postmarketing with Zinc Sulfate Injection when used as recommended for the approved indication.

QT

A through QT study has not been conducted by the Applicant. An Information Request was sent to the Applicant on April 29, 2019, requesting a written assessment of the potential for zinc sulfate to prolong the QT interval. The Applicant was requested to provide any *in vitro* or nonclinical information available on the potential for zinc to delay ventricular repolarization. The Applicant responded on May 13, 2019 that they have reviewed the available published literature reporting zinc and its effect on the cardiovascular system, and have not identified any *in vitro* or nonclinical data regarding the potential for zinc to delay ventricular repolarization. They cited three studies in rats (124-126) and two studies reporting ingested zinc doses that exceeded the daily recommended dietary allowance (127, 128). The Applicant was also requested to review the literature and provide any additional information on the potential for intravenous and/or oral zinc to prolong the QT interval in humans. The Applicant responded

that they are not aware of any report of QT prolongation or related cardiac adverse events in literature studies or postmarketing case reports.

8.2.5. Integrated Assessment of Safety

The assessment of safety for parenteral zinc as a source of an essential element is based entirely on published literature for adult and pediatric populations. Given that most studies that reported safety data were not intended to assess the safety of parenteral zinc as a nutritional supplementation, these publications can only serve to elucidate overt adverse effects. Interpretation of available safety findings in the published literature that reported on adverse events of patients receiving parenteral zinc is also challenging because the sample size across studies that reported on safety outcomes is relatively small. The 4 adult studies enrolled a total of 127 patients; the 2 pediatric studies enrolled a total of 30 patients (see Section 8.2.2 Review of the Safety Database).

Despite the paucity of safety information in published literature, it can be concluded that the recommended adult and pediatric age and body-weight adjusted dosage for Zinc Sulfate is below the UL for oral zinc (see Section 8.4 Summary of Dosing Recommendations) based on the following observations:

- The IOM established the following ULs for oral zinc by age: 40 mg/day (adults), 4 mg/day (0 to 6 months of age), 5 mg/day (7 to 12 months of age), 7 mg/day (1 to 3 years of age), 12 mg/day (4 to 8 years of age), 23 mg/day (9 to 13 years of age), and 34 mg/day (14 to 18 years of age).
- Unapproved but marketed parenteral zinc has been used in clinical practice for close to 40 years without reports of significant adverse events.
- No reports of significant adverse events in adult clinical studies attributed to parenteral zinc supplementation at a dose of 8 mg/day for 64 weeks and at a dose of 26 mg for 8 days.
- No reports of significant adverse events in pediatric studies attributed to parenteral zinc supplementation at a dose of up to 0.75 mg/kg/day for 7 days (age range 1 month to 10 years).

In summary, the published trials and clinical experience provide extensive safety experience on intravenous administration of zinc sulfate as an additive to PN in patients on long-term PN , although with noted limitations. There has also been considerable post-marketing experience of marketed, unapproved parenteral zinc sulfate . Additionally, clinical studies and post-marketing reports have not conclusively identified zinc-related adverse reactions in patients receiving intravenously administered PN-solutions containing intravenous zinc sulfate within the recommended dosage range. Therefore, it can be concluded that there appear to be few, if any, adverse reactions at the recommended age-and body weight-adjusted dosing regimen (see Section 8.4 Summary of Dosing Recommendations).

8.3.Statistical Issues

Not applicable.

8.4.Summary of Dosing Recommendations

The age-and body weight-adjusted dosing regimen below is recommended:

Table 9: FDA Recommended Dosage Regimen for Zinc Sulfate Injection

Preterm Neonates	Term Neonates	Pediatrics		Adults
<3 kg	3-5 kg	5-10 kg	>10 kg	
400 mcg/kg/day	250 mcg/kg/day	100 mcg/kg/day	50 mcg/kg/day (not to exceed 3 mg/day)	3 mg/day

8.5.Conclusions and Recommendations

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

Zinc is an essential TE obtained primarily through diet that is required to maintain human health. Zinc Sulfate Injection is supplied in two concentrations containing 3 or 5 mg/mL of elemental zinc. Since 1984, zinc has been routinely added to PN solutions. The FDA has previously approved the following products containing zinc: (i) Zinc chloride injection 1 mg/mL by Hospira Inc. (NDA 18959; currently available); (ii) Zinc Sulfate Injection 1 mg/mL by Abraxis Pharm. (NDA 19229; withdrawn on 10/11/16). However, the Applicant currently markets "Concentrated Zinc Sulfate Injection" (contains 5 mcg/mL of elemental zinc) as an unapproved product and it has been used for close to 30 years "as a supplement to intravenous solutions given for TPN."

The Applicant has not conducted any clinical trials of their product. They are relying on literature including randomized, placebo and active-controlled clinical trials in a range of patient populations (neonatal, pediatric, and adult), that primarily evaluate systemic concentrations of zinc in response to intravenous zinc supplementation in patients receiving PN.

Overall, the data supports the efficacy of doses of 3 mg/day for metabolically stable adult patients receiving PN and 50 mcg/kg/day (up to 3 mg/day) for pediatric patients weighing ≥10 kg, 100 mcg/kg/day for pediatric patients weighing 5 kg to <10 kg, 250 mcg/kg/day for term neonates weighing 3 kg to <5 kg, and 400 mcg/kg/day for preterm neonates weighing <3 kg. For the pediatric dosage rationale see Section 10 Pediatrics. This dosage is anticipated to meet the nutritional requirements of most patients on PN. However, the dosage must be individualized accounting for the patient's clinical condition, nutritional requirements, and other sources of zinc intake either orally or enterally. Some patients will have higher clinical requirements, most

notably those with small bowel fluid loss or excess stool or ileostomy output. Periodic monitoring of systemic zinc concentrations, along with clinical examination, should be considered to avoid clinical deficiency.

The safety database includes information from clinical trials and post-marketing adverse event reports of intravenous zinc sulfate at and above the recommended clinical dosage. Despite some limitations to the safety information available from clinical studies, due to lack of rigorous data collection and reporting, there appear to be few, if any, adverse reactions within the recommended dosage range. The safety margin is further supported by the ULs for oral zinc by age.

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

9 Advisory Committee Meeting and Other External Consultations

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

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

The Council agreed with the Division that there is substantial evidence that zinc is a required TE for health maintenance and recognized the challenges in identifying the optimal parenteral dose and the uncertainties of dosing in special populations. The Council agreed with DGIEP's approach to approve the proposed Zinc Sulfate Injection product for the indication 'as a source of' selenium for PN in adult and pediatric patients based on collective evidence including clinical data on selenium supplementation in PN patients, known enteral nutritional requirements (e.g., Recommended Dietary Allowance, Reference Daily Intake (RDA, RDI)), estimated relative bioavailability of oral versus intravenous administration, current clinical PN guidelines, the available toxicity data, as well as the time and extent of use in clinical practice.

No Advisory Committee Meeting or External Consultations was conducted.

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

The Division of Epidemiology I assessed a systematic literature review submitted by the Applicant in support of NDA 209377. For details, please see the complete consult review filed in DARRTS by Drs. J. Weissfeld, P. Bright, and S.K. Sandhu on April 30, 2019.

DEPI found that:

- The Applicant commissioned a systematic literature review, conducted by the (b) (4) and reported by the Applicant as stipulated by pre-NDA negotiations with DGIEP.
- (b) (4) identified 100 articles by systemic search for medical literature about patients given zinc parenterally or zinc status in patients on PN.
- The medical literature found by (b) (4) presented no evidence for toxicity or other serious adverse consequences from zinc when administered intravenously for PN at conventional doses.

Expanding the (b) (4) search strategy, DEPI identified 57 additional articles not captured by (b) (4) A DEPI review of these additional articles supported conclusions reached by the Applicant about the safety of zinc for PN.

10 Pediatrics

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

- Zn is an essential trace element that performs multiple physiological roles in a variety of catalytic, structural, and regulatory processes
- Zn is primarily provided through the diet; therefore, in patients unable to tolerate enteral feeds, Zn must be provided parenterally to meet the nutritional needs
- There are well-described symptoms associated with Zn deficiency in pediatric patients such as acrodermatitis enteropathica, as well as reported alopecia, diarrhea, growth retardation, delayed sexual maturation, eye and skin lesions and skeletal myopathy. These manifestations of zinc deficiency demonstrate the importance of ensuring that pediatric patients in the full age range are receiving adequate amounts of Zn to support body processes
- The IOM recognizes the importance of receiving adequate amounts of Zn enterally and has established age-based reference standards for daily Zn intake for the full pediatric age range down to birth, including term neonates
- Published clinical guidelines from professional organizations have endorsed the use of Zn as a PN additive for over 40 years
- FDA approved other parenteral zinc products (zinc chloride and zinc sulfate) for use as a source of Zn in PN in the pediatric population in 1986 and 1987, respectively
- Administration of intravenous zinc in PN helps to maintain zinc serum levels and to prevent depletion of endogenous stores, and subsequent deficiency symptoms.
- There are no reports of toxicity in adult or pediatric patients receiving intravenously administered PN solutions containing zinc sulfate within the recommended dosage range (129) despite the extensive time and extent of use

As noted in Section 1.1, FDA has previously approved the following two zinc products under the 505(b)(2) pathway as exclusively literature-based NDAs for a similar indication to that proposed for Zinc Sulfate Injection:

- Zinc Chloride Injection, 1 mg/mL (Hospira, Inc., NDA 018959, approved on 6/26/1986)
- Zinc Sulfate Injection, 1 mg/mL (Abraxis Pharmaceutical Products, NDA 019229, approved on 5/5/1987 but later voluntarily withdrawn from the market for reasons that are not related to safety or efficacy)

Table 10: Approved Dosage Regimen for Both Currently Approved Zinc Products

Age	Zinc Dosage
Adult	2.5 to 4 mg/day
Term to 5 years	100 mcg/kg/day
Preterm	300 mcg/kg/day

Source: Created by FDA reviewer based on Zinc Chloride Injection and Zinc Sulfate Injection labeling retrieved from DailyMed

Although the Applicant is not relying on either of these products as a listed drug to support this 505(b)(2) application, the review team considered the publications submitted to support the prior zinc approvals, all of which were published prior to 1982, for NDA 019229. However, the majority of primary articles and controlled trials submitted in this application for the proposed product were published after 1982, which justifies the differences between the proposed and approved dosing recommendations.

The review team evaluated the Applicant's proposed dosing recommendations in the context of age-based daily parenteral zinc requirements (mcg/kg/day) calculated for the pediatric population up to 1 year of age from the following factors: growth requirements, endogenous fecal losses, urine excretion and sweat losses. Table 11 describes these factorial calculations for total intravenous zinc requirements for preterm and term infants.

Table 11: Factorial Calculations of Intravenous Zinc Requirements in Infants*

	Intravenous zinc requirements (mcg/kg/day)				
	Preterm	**Term**			
		1 mo	**3 mo**	**6 mo**	**12 mo**
Growth requirements (130) (131)	250	175	85	45	30
Endogenous fecal losses (7)	25	10	[10]	10	[10]
Urine excretion	40	40	[20]	10	20
Sweat losses**	Copyright Material				
Total intravenous requirements	325	235	115	75	60

Source: Greene (1988) (132)
Abbreviations: mo=month
*Values in brackets are not based on actual measurements. The publication did not specify the basis for the estimated values for sweat losses across all ages listed in the table. Estimated values for endogenous fecal losses and urine excretion for which actual measurements are not available were interpolated based on the pattern of data for the respective sources of zinc loss in the younger and older age groups.
** Copyright Material , unpublished observations.

The review team then sought to determine if the publications included in this application supported the safety and efficacy of these age-based requirements. As described in Section 8.1.3 and Section 8.1.5, the team concluded that clinical studies in neonates have confirmed that this subpopulation has higher zinc requirements than older children and adults; moreover, preterm neonates have higher zinc requirements than term neonates. Therefore, these studies support the factorial calculations outlined in Table 11. Widdowson et al. demonstrated that two thirds of an infant's zinc is transferred from the mother during the last 10 to 12 weeks of normal gestation (133). Neonates born prior to 30 weeks gestational age may not benefit from this maternal transfer of zinc. Therefore, they must receive larger quantities of zinc to replace ongoing losses and build up body stores to meet the needs of rapid protein synthesis and prevent growth impairment. The zinc requirements of neonates have also been supported by balance studies conducted by Zlotkin (7), Lockitch (10, 94), and James et al. (9) (see Section 8.1.3), which examined the amounts of zinc retained following intravenous administration in term and preterm infants. The review team also determined the 5th and 95th percentile weights for each age listed in Table 11 to identify the weight range corresponding to each age-related parental zinc requirement (see Table 15 below). The review team concluded that

pediatric dosing for Zinc Sulfate Injection targeting provision of the following would allow daily zinc requirements to be met based on age and weight: 400 mcg/kg/day in preterm neonates, 250 mcg/kg/day in term neonates up to 3 months of age, 100 mcg/kg/day for patients greater than 3 months of life but weighing less than 10 kg, and 50 mcg/kg/day for pediatric patients weighing greater than 10 kg.

For patients greater than 3 months, the review team identified three clinical studies (4-6) that supported the factorial calculations made by Greene et al (132). However, these studies included a limited number of patients spanning a wide age margin and study duration (see Section 8.1.3).

Therefore, the review team also considered the assessment of intravenous zinc requirements determined by the IOM to establish their reference standards for daily zinc intake. Similar to Greene et al. (132), the IOM performed factorial calculations of the intravenous zinc requirements (mcg/day) to replace intestinal, urinary, and integumental losses and meet growth requirements based on age for patients 7 months and older. The IOM used these calculations in addition to an estimated fractional absorption value (i.e., oral bioavailability) to determine their RDA and RDI values for oral intake of zinc. However, multiple factors can impact zinc absorption from the GI tract, resulting in variability in oral bioavailability ranging from approximately 30% to up to 80%. This wide range in oral bioavailability makes estimating parenteral zinc requirements on the basis of enteral zinc intake alone challenging. Therefore, an estimation of the parenteral zinc dose based on the factorial analysis of zinc requirements obviates the need to factor in the oral bioavailability. Table 12 outlines the IOM's calculation of zinc requirements for infants and children 7 months of age and older and estimates weight-based dosing for children in the 5^{th} and 95^{th} percentiles per CDC growth charts. The proposed dosing of 100 mcg/kg/day for patients greater than 3 months of life but weighing less than 10 kg falls within calculated parenteral dosing to meet zinc requirements for children 7 to 12 months (i.e., 68.5 to 122 mcg/kg/day). The proposed dose of 50 mcg/kg/day for pediatric patients weighing greater than 10 kg is also consistent with calculated needs for children approximately 1 year of age and older (i.e., 29.3 to 93 mcg/kg/day). Clinical studies by Ricour 1977 (5), Lowry 1981 (4) and Dahlstrom 1986 et al. (6) also support that zinc requirements continue to fall for patients outside the neonatal period and into childhood down to 50 to 100 mcg/kg/day for patients greater than 1 year of age.

Table 12: Factorial Calculations of Intravenous Zinc Requirements for Infants and Children 7 Months and Older

Age	Zinc Requirement (mcg/day)	Weight range 5th percentile	Parenteral Dose for 5th percentile (mcg)/kg/day	Weight range 95th percentile	Parenteral Dose for 95th percentile (mcg)/kg/day
7-12 months	836	6.85-8.18	122-102	10.7-12.2	78.1-68.5
1-3 years	744	8.44-13.22	88-56	12.6-17.4	59.0-42.8
4-8 years	1196	13.35-21.83	90-55	20.3-34.9	58.9-34.2
9-13 years	2120	22.70-37.88	93-56	35.3-72.2	60.1-29.3
14-18 years	3372 boys	38.48-53.06	88-64	72.7-91.8	46.4-36.7
	2936 girls	37.91-45.30	77-65	72.4-80.6	40.6-36.4

Source: Adapted from the Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc: A Report of the Panel on Micronutrients, Subcommittees on Upper Reference Levels of Nutrients and of Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. 2001 and CDC growth charts

In determining pediatric dosing recommendations for this product, the review team also considered dosing accepted by clinicians from long-standing clinical guidelines. The Applicant's proposed dosing generally follows the ASPEN clinical dosing guidelines (35). The ASPEN guidelines contain updated clinical dosing regimens and RDA with respect to maintaining zinc homeostasis, and are currently used by hospitals and ICUs in the United States. The guidelines represent the expert opinions from the Board Directors of ASPEN and from the Multi-Trace Element Working Group members in the field of PN based on published literature.

Table 13: ASPEN Weight-Based Zinc Dosing Regimen for Pediatric Patients (2019) (36)

Trace Element	Preterm Neonates <3 kg (mcg/kg/d)	Term Neonates 3-10 kg (mcg/kg/d)	Children 10-40 kg (mcg/kg/d)	Adolescents >40 kg (per Day)
Zinc	400	250	50	2 mg to 5 mg

Source: Appropriate Dosing for Parenteral Nutrition: ASPEN Recommendations (January 2019) (36)

DGIEP recommends the following age- and body weight-adjusted dosing regimen for the pediatric population with the supportive publications listed in the right column:

Table 14: Recommended Dosage of Zinc Sulfate Injection for Pediatric Patients by Age and Estimated Weight With Supportive Publication Information

Population	Estimated Weight for Age*	Recommended Daily Dosage	Supportive Publication
Pediatric patients	10 kg and above	50 mcg/kg (up to 3 mg/day)	Ricour 1977 (5) (50-100 mcg/kg/day)
Pediatric patients	5 to 10 kg	100 mcg/kg	Dahlstrom 1986 (6)/Lowry 1981 (4) (70 to 80 mcg/kg/day)
Term neonates	3 to 5 kg	250 mcg/kg**	Zlotkin 1983 (7) (>150 mcg/kg/day) Suita 1984 (8) (40 mcg/kg/day)
Preterm neonate	<3 kg	400 mcg/kg	James 1979 (134) (200 mcg/kg/day) Lockitch 1983 (94); 1985 (10) (400 mcg/kg/day) Zlotkin 1983 (7) (438 mcg/kg/day) Friel 1984 (11) (350 mcg/kg/day) Huston 1991 (110) (>280 mcg/kg/day)

Source: Created by FDA reviewer
*Approximate weight based on CDC growth charts
**term neonates have higher requirements in the first 3 months of life

The following safety and efficacy conclusions were made to support our proposed dosing recommendations:

- Our review of currently available dosing information in the literature demonstrates that the dose levels and dosing regimens recommended by ASPEN are supported by controlled clinical studies with effectiveness and safety information. The review team has identified ten (4-8, 10, 11, 94, 110, 134) controlled clinical trials in the published literature that studied doses similar to what are recommended above and cover all the pediatric age (weight) groups in the table.
- Published zinc requirements (132) and balance studies confirm that neonates require more zinc input to balance urinary losses and provide a guideline to support dosing in patients up to 1 year of age (9, 30, 94).
- The proposed dosing recommendations correlate with the required amount of absorbed zinc (mcg/day) established by the IOM for zinc for patients 7 months of age and older.
- Because of the noted clinical manifestations of zinc deficiency, the priority is to ensure adequate dosing to meet the nutritional needs of pediatric patients, particularly the youngest patients who have increased requirements.
- Zinc-related adverse reactions have not been reported in clinical studies or postmarketing reports in patients receiving intravenously administered PN solutions containing zinc sulfate within the recommended dosage range and up to 824 mcg/kg/day (131)in pediatric patients.
- The proposed dosing is aligned with clinical guidelines that are currently used in medical practice and are supported by time and extent of use for over 4 decades.
- Labeling will advise prescribers to individualize the dosing as needed based on the patient's requirements and will recommend monitoring of zinc serum

concentrations during treatment along with clinical monitoring of all patients for signs and symptoms of zinc deficiency.

Table 15: Summary of Proposed Dosing Recommendations and ASPEN Guidelines

Age	5th weight percentile*	95th weight percentile*	Total IV Zinc Requirements	Applicant Proposed Dosing	FDA Proposed Dosing	ASPEN Guidelines
Preterm			325 mcg/kg/day	400 mcg/kg/day (b) (4) 3 kg)	400 mcg/kg/day (preterm neonates <3 kg)	400 mcg/kg/day (<3 kg)
1 month	3.4 kg	5.4 kg	235 mcg/kg/day	250 mcg/kg/day (3-5 kg)	250 mcg/kg/day (term neonates 3 kg to <5 kg)	250 mcg/kg/day (3-10 kg)
3 months	4.8 kg	7.4 kg	115 mcg/kg/day	(b) (4) 100 mcg/kg/day (>5 to 10 kg)	100 mcg/kg/day (pediatric patients 5 kg to <10 kg)	
6 months	6.5 kg	9.6 kg	75 mcg/kg/day			
12 months	8.6 kg	12.4 kg	60 mcg/kg/day	50 (b) (4) mcg/kg/day (b) (4) 10 kg)	50 mcg/kg/day (max 3 mg/day) (pediatric patients 10 kg and above)	50 mcg/kg/day (10-40 kg)
Adults				3 mg	3 mg	2.5 mg to 5 mg

Source: Created by FDA reviewer

Because the proposed dosing recommendations are intended to serve as a safe starting dose with the plan to individualize dosing as needed, the review team considered whether the proposed dosing recommendations provide a margin of safety. The review team also sought to determine if a maximum safe daily dose should be added to labeling based on available information but did not identify any safety data to support such a recommendation. The IOM has established the tolerable upper intake level (UL) for total daily intake of Zn from food, water and supplements, which is the highest level of oral daily zinc intake that is likely to pose no risk of adverse effects for almost all healthy people. The adverse effect of excess zinc on copper metabolism (i.e., reduced copper status) was chosen as the critical effect on which to base the UL. However, the uncertainty as to whether the effect of zinc on copper is applicable when zinc is administered by routes other than oral limits the generalizability of the UL to parenterally-administered zinc. The review team identified no zinc related adverse reactions in the published literature, from post-marketing safety surveillance, and over the decades of clinical experience with parenteral zinc at the proposed doses.

The NDA for Zinc Sulfate Injection triggers the PREA as a new dosing regimen not previously approved by FDA for the proposed indication. The Applicant must provide a pediatric assessment that addresses the entire pediatric population, which includes providing an age-appropriate formulation. The Applicant is attempting to fulfill their PREA requirement by including data in this application to support product approval in the full pediatric age range from birth to less than 17 years of age. However, the concentration of the Applicant's proposed formulation would require admixture of very small volumes as low as 0.07 mL, and automated equipment cannot accommodate admixture of volumes less than 0.2 mL. Accordingly,

administration using the current formulation would preclude admixture using automated equipment for some pediatric patients weighing <12 kg based on the anticipated weight-based dosing recommendations.

Table 16: FDA Proposed Dosing Recommendations

Population	Estimated Weight for Age*	FDA Recommended Daily Dosage	Weight range that would require admixture of an administration volume <0.2 mL for 3000 mcg/mL Zinc solution based on FDA proposed dosing
Pediatric patients	10 kg and above	50 mcg/kg (up to 3 mg/day)	10-12 kg
Pediatric patients	5 to 10 kg	100 mcg/kg	5-6 kg
Term neonates	3 to 5 kg	250 mcg/kg**	2.4 kg
Preterm neonate	<3 kg	400 mcg/kg	0-1.5 kg

Source: Created by FDA reviewer

The Agency notes the following concerns: (1) the feasibility of accurately administering the intended dose in such a small volume, particularly in healthcare settings that do not have automated equipment; (2) the potential for decreased sterility and introduction of medical errors with manual manipulation or intermediate dilutions of the product prior to mixing into PN. The Agency acknowledges that admixing of dosing volumes as low as 0.01 mL can be performed manually using graduated 1 mL syringes, which are widely available in healthcare settings, and that this approach is the standard of care when automated equipment is either unavailable or unable to accommodate admixture of very small volumes (i.e., <0.2 mL). Nevertheless, the utility of a less concentrated formulation for neonates and pediatric patients weighing less than 12 kg includes the following: (1) allows precise dosing and titration with automated equipment in admixing PN; (2) improves sterility by limiting the need for manual manipulation; (3) minimizes dosing errors potentially introduced with manual manipulation. Development of a less concentrated age-appropriate formulation that could be readily admixed for PN by automated equipment would help mitigate this risk for medication errors and enhance dosing accuracy for the youngest and lightest weight patients. Accordingly, the review team plans to label the product down to birth but will issue a post-marketing requirement under PREA to the Applicant to provide an age-appropriate formulation for pediatric patients weighing less than 12 kg. DGIEP will consider the pediatric assessment for patients weighing less than 12 kg to be complete once this age-appropriate formulation is developed.

Of note, the Applicant is currently seeking approval for two adult concentrations (3 mg Zn/mL and 5 mg Zn/mL). (b) (4)

In accordance with the 2019 Pediatric Labeling Guidance, the Pediatric Use subsection must include a pediatric use statement or reasonable alternative statement when a drug is approved in pediatric patients for an indication that is the same as an approved indication in adults. Because this approval is exclusively based on published data, a use statement that conveys that

Zinc Sulfate Injection is approved in the pediatric population, including neonates, for the proposed indication, in addition to a statement that describes the basis for safety and dosing would be appropriate. Additionally, the Pediatric Use subsection should highlight adverse reactions that occur at a different frequency or severity than in adults. Accordingly, labeling should describe the increased risk of aluminum toxicity in preterm neonates with a cross-reference to a more detailed description in the corresponding Warnings and Precautions subsection. Additionally, as noted in Section 5.5.5, the safety assessment of aluminum exposure with this product does not exceed the limit established for daily patient exposure from all potential sources of aluminum in a TPN admixture of 5 mcg/kg/day (76).

11 Labeling Recommendations

11.1. Prescription Drug Labeling

- The Applicant's original proposed Proprietary Name "(b) (4)" was determined to be unacceptable by DMEPA due to potential for confusion with the currently marketed product (b) (4)) based on orthographic and phonetic similarities and overlapping product characteristics. The Applicant subsequently withdrew the proprietary name and plan to market the product under the established name "Zinc Sulfate Injection."
- **Section 2 Dosage and Administration**: The drug product is supplied as a Pharmacy Bulk Package vial that is for admixing in PN. It is not for direct intravenous infusion. Therefore, information on preparation, administration, admixing, stability and storage of PN solutions containing zinc was included in this section. In addition to the recommended dosage in adults and pediatrics (see 1st page of the Unireview for the complete dosing regimen), it is noted that dosing should be individualized based on patient's clinical condition and systemic zinc concentrations should be monitored. Patients should also be monitored clinically for signs and symptoms of zinc deficiency, especially pediatrics. The lower end of the reported range of zinc concentrations in healthy adults in the U.S. is included (60 mcg/dL) with the recommendation that interpretation of individual patient results should be performed in the context of the current laboratory reference range. It is also noted that zinc concentrations may vary depending on the assay used and the laboratory reference range. Therefore, collection, processing, and storage of the blood samples for zinc analysis should be performed according to the laboratory's sample requirements. Zinc concentrations in hemolyzed samples are falsely elevated due to release of zinc from erythrocytes.
- **Section 4 Contraindications:** This section was updated to include a statement to avoid use in patients with a known hypersensitivity to zinc.
- **Section 5 Warnings and Precautions:** This section was updated to include pertinent PN product class safety information including pulmonary vascular precipitates, vein damage and thrombosis, aluminum toxicity (as required by 21 CFR 201.323) and laboratory monitoring. It is noted that these subsections are not specifically applicable to the zinc component of PN but are more general class labeling language for PN solutions in general. Additionally, this section was updated to include copper deficiency and zinc hypersensitivity in association with the use of zinc-containing products administered by other routes of administration (e.g., oral, subcutaneous).
- **Section 6 Adverse Reactions:** The review did not identify any zinc-related adverse reactions reported in clinical studies or postmarketing reports in patients receiving intravenously administered PN-solutions containing zinc within the recommended dosage range. This section was updated to include copper deficiency and zinc hypersensitivity in association with the use of zinc-containing products administered

by other routes of administration (e.g., oral, subcutaneous). (b) (4) [redacted]

- **Section 7 Drug Interactions:** This section was deleted because the interactions is not clinically relevant with zinc sulfate when administered in PN.
- **Section 8 Use in Specific Populations:**
  - Pregnancy, Lactation: These sections were written per PLLR format and content using the nonclinical and clinical data described elsewhere in this review.
  - Pediatric Use: The product is approved for use in the entire pediatric population (birth to less than 17 years) and the risk of aluminum toxicity in preterm infants is described.
- **Section 10 Overdosage:** This section was updated to include details from intravenous zinc overdosage cases of adults and a preterm infant identified in the medical literature.
- **Section 12 Clinical Pharmacology:**
  - Mechanism of Action: The role of zinc in various biological functions is described in broad terms
  - Pharmacodynamics: There are no known zinc sulfate exposure-response relationships
  - Clinical Pharmacology: The distribution and elimination of zinc are described.
- **Section 13 Nonclinical Toxicology:** This section was removed. No toxicology data exist with intravenous zinc sulfate.
- **Section 14 Clinical Studies:** This section was removed (b) (4) [redacted]

Please see the approved label for final agreed-upon labeling.

12 Risk Evaluation and Mitigation Strategies

REMS was not recommended. The benefit-risk profile for Zinc Sulfate Injection is favorable, and any potential risks can be mitigated through product labeling (see Section 11). There are no additional risk management strategies required beyond the recommended labeling.

13 Postmarketing Requirements and Commitment

As discussed in Section 10, a PREA PMR will be issued to the Applicant to provide an age-appropriate formulation to ensure accurate dosing volumes of Zinc Sulfate Injection for pediatric patients weighing less than 12 kg. The Applicant has agreed to the following PMR:

3663-1 Develop an age-appropriate formulation to ensure accurate dosing by volume for pediatric patients weighing less than 12 kg

Final Report Submission: 08/2021

14 Division Director Comments

I concur with the recommendation of the review team that the benefits outweigh the risks for this NDA seeking an indication for the use of Zinc Sulfate Injection in adult and pediatric patients as a source of zinc for PN when oral or enteral nutrition is not possible, insufficient, or contraindicated, and that this NDA should be approved.

Zinc is a trace element that is naturally present in the diet. It is well-established as an essential trace element, and functions as a component of various enzymes that are responsible for DNA replication, RNA transcription, and protein synthesis. Clinical manifestations of zinc deficiency have been described, and recognition of the need for zinc supplementation in patients who do not obtain adequate oral intake, and initial studies evaluating zinc supplementation in PN, date back to the 1970s. Zinc injections for use in PN were initially approved based on published literature in the 1980's. However, at present, the only available FDA-approved product is zinc chloride injection (NDA 18-959), although an unapproved zinc sulfate injection product is on the market. While not currently in drug shortage, injectable zinc has been considered a drug-shortage product in the past.

In pre-NDA discussions, the Division discussed with the Applicant a systematic review approach to compile a literature framework to support the safety and efficacy of the product for the proposed indication. Of note, the absence of controlled studies evaluating clinical efficacy outcomes associated with zinc supplementation warrant a "source of" indication, (b) (4) . Such a general literature-based approach was also discussed with the MPPRC in February 2019, which was in agreement with this approach, noting that it is important to avail patients of a quality-controlled product based on the best available evidence.

As discussed comprehensively in this review, consideration of efficacy data from published clinical trials of intravenous zinc sulfate in the PN setting; nutritional requirements of oral/enteral zinc (i.e., RDA, RDI values); PN guidelines based on expert consensus; time and extent of use in clinical practice; and generally accepted scientific knowledge of zinc as an essential trace element, support a finding of substantial evidence of effectiveness of Zinc Sulfate Injection for the proposed indication in adult and pediatric patients. Measurement of zinc levels serves as an acceptable surrogate efficacy endpoint based on the general scientific knowledge that low zinc levels are associated with adverse clinical outcomes, and that supplementation of zinc in PN can increase or maintain zinc concentrations. In clinical practice, the clinical effect of supplementation on patients can be appropriately monitored using a combination of serum zinc concentrations and clinical signs and symptoms.

With respect to safety, the recommended adult and pediatric age and body-weight adjusted dosage for Zinc Sulfate is below the UL for oral zinc with the expected oral bioavailability of zinc taken into consideration. The safety assessment with respect to aluminum exposure

determined that the product does not exceed the limit established for total exposure from all potential sources of aluminum in a TPN admixture.

Because this NDA represents a new dosing regimen, PREA was triggered. The review team and PeRC determined that the pediatric assessment was complete aside from very small pediatric patients, for whom an age-appropriate formulation may be needed in order to permit admixture of very small volumes via automated admixing equipment. The age-based dosing for neonates and pediatric patients weighing under 12 kg would entail administration of a dose volume < 0.2 mL for the 3 mg/mL concentration. While such a dose can be administered manually using a graduated 1 mL syringe, development of a less concentrated formulation that would permit automated admixing would enhance safe and effective use. Therefore, the Applicant will be issued a PMR to develop an age-appropriate formulation for such lower weight pediatric patients.

15 Appendices

15.1. Financial Disclosure

No clinical data submitted.

15.2. OCP Appendices (Technical documents supporting OCP recommendations)

N/A

15.3. Additional Clinical Outcome Assessment Analyses

N/A

15.4. References

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15.5. Signature Pages

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Supervisory Pharmacologist	Sushanta Chakder	OND/ODEIII/DGIEP	**Sections: 5** **Reviewed/Edited: 5** **Appendices:** **None**	**Select up to two:** ___Authored _X_Cleared
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