CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209376Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 209376
Assessment 1

Drug Product Name	Tralement (Trace Elements Injection 4*, USP)
Dosage Form	Injection
Strength	1 mL in a single-dose vial. Each mL contains zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	American Regent, Inc., Shirley, NY
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	9/5/2019	OPQ
Amendment	11/20/2019	OPQ, Microbiology
Amendment	12/23/2019	ONDP
Amendment	1/10/2020	ONDP
Amendment	1/14/2020	ONDP
Amendment	2/21/2020	ONDP
Amendment	2/28/2020	OPMA
Amendment	4/10/2020	OPMA
Amendment	4/13/2020	ONDP
Amendment	4/24/2020	ONDP
Amendment	4/28/2020	ONDP, API
Amendment	5/15/2020	ONDP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Friedrich Burnett	Donna Christner
Drug Product	Jane Chang	Moo-Jhong Rhee
Manufacturing /Facilities	Kejun Cheng	Aditi Thakur
Microbiology	Bethanie Lee	Jesse Wells
Biopharmaceutics	N/A	N/A
Environmental Assessment	Jane Chang	Moo-Jhong Rhee
Regulatory Business Process Manager	Oumou Barry	
Application Technical Lead	Hitesh Shroff	
Laboratory (OTR)	N/A	N/A

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Tralement (trace elements injection 4*). * Each mL provides: zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made a final overall "Approval" recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The label/labeling issues have been resolved satisfactorily from the CMC perspective.

Therefore, from the OPQ perspective, this NDA is recommended for Approval.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Tralement delivers Zinc, Copper, Manganese and Selenium elements. Tralement is a fixed dose combination product containing four trace elements.

Tralement is a sterile, non-pyrogenic, clear, and colorless to slightly blue solution, intended for use as a combination of four trace elements and an additive to intravenous solutions for parenteral nutrition. It contains no preservatives (b) (4).

It is supplied in 1 mL single-dose glass vials. Each mL of solution contains zinc 3 mg (equivalent to zinc sulfate 7.41 mg), copper 0.3 mg (equivalent to cupric sulfate 0.75 mg), manganese 55 mcg (equivalent to manganese sulfate 151 mcg), selenium 60 mcg (equivalent to selenious acid 98 mcg), and water for injection.

Tralement is not for direct intravenous infusion. Prior to administration Tralement must be used as an admixture in parenteral nutrition solution.

Proposed Indication(s) including Intended Patient Population	Tralement is a fixed-dose combination of four trace elements indicated in adult and pediatric patients weighing at least 10 kg as a source of zinc, copper, manganese, and selenium for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.
Duration of Treatment	As long as needed
Maximum Daily Dose	Tralement is recommended only for patients who require supplementation with all four of the individual trace elements (i.e., zinc, copper, manganese and selenium).

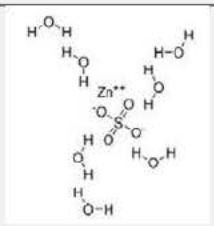
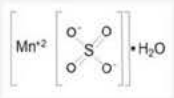
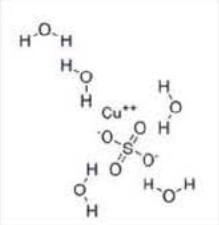
	Adults and Pediatric Patients Weighing at least 50 kg: The recommended dosage of Tralement is 1 mL per day added to parenteral nutrition Tralement is not recommended for adults or pediatric patients weighing less than 10 kg who may require a lower dosage of one or more of the individual trace elements. Pediatric Patients Weighing 10 kg to 49 kg: The recommended dosage of Tralement added to parenteral nutrition is 0.2 mL to 0.8 mL per day by pediatric weight. For pediatric patients 10 kg to 49 kg who may require a higher dosage than provided by Tralement of one or more of the individual trace elements, use additional single-ingredient trace element products.
Alternative Methods of Administration	N/A

Quality Assessment Overview

Drug Substances: Adequate

Drug Substance:

The active ingredients in Tralement (trace elements injection 4*) are Zinc sulfate, USP; Cupric sulfate, USP; Manganese sulfate, USP and Selenious acid, USP.

Drug Substance	Structure	Manufacturer	Physico/Chemical Properties
Zinc sulfate, USP $ZnSO_4 \cdot 7H_2O$ Molecular weight: 287.54 g/mol		(b) (4)	• Colorless, odorless, granules or crystals • Soluble in water, insoluble in alcohol, efflorescent in dry air • log P = -0.84 • Two polymorphs reported in literature
Manganese sulfate, USP MnSO4. H2O Molecular weight: 160.01 g/mol			• Pale pink odorless crystalline powder • Soluble in water, insoluble in alcohol • Slightly efflorescent • pKa = -3
Cupric sulfate, USP $CuSO_4 \cdot 5H_20$ Molecular weight: 249.69 g/mol			• Deep blue triclinic crystals or blue granules or powder • Solubility varies with pH. Insoluble hydroxides form above pH 7.0 • Hygroscopic at high humidity • pKa = -3
Selenious Acid, USP H_2SeO_3 Molecular weight: 128.97 g/mol			• Colorless, white crystals • Soluble in water and alcohol • Hygroscopic • $pK_{a1} = 2.62$ • $pK_{a2} = 8.32$

All four drug substances used in the drug product formulation are of USP grade. The detailed CMC information including physicochemical properties, manufacturing process, characterization, specification, Certificate of Analysis, container closure system and stability of the drug substances are provided in the DMFs from the manufacturers of Zinc sulfate, USP and Manganese sulfate, USP and in this application for Cupric sulfate, USP and Selenious acid, USP. The letters of authorization were provided. The DMFs were reviewed and deemed adequate.

The CMC information was reviewed by the drug substance reviewer, Dr. Friedrich Burnett, and was concluded that the submitted information is adequate to support the drug product, Tralement. (see the **Drug Substance** review).

The Office of Process and Facilities (OPF) has made an "Adequate" recommendation for all drug substance manufacturing and testing facilities. (See the **Manufacturing Integrated Assessment** review)

Drug Product: Adequate

Tralement (trace elements injection 4*) is a sterile, non-pyrogenic, clear and colorless to slightly blue solution for intravenous use to deliver zinc, copper, manganese and selenium elements as additives to parenteral nutrition. This product is not for direct intravenous infusion so it must be diluted with parenteral nutrition prior to administration. It is supplied as 1 mL vials. Each mL of solution contains zinc 3 mg (equivalent to zinc sulfate 7.41 mg), copper 0.3 mg (equivalent to cupric sulfate 0.75 mg), manganese 55 mcg (equivalent to manganese sulfate 151 mcg), selenium 60 mcg (equivalent to selenious acid 98 mcg), and water for injection. Sulfuric acid may be added to adjust pH between 1.5 and 3.5. All ingredients are of USP/NF grade and there are no preservatives (b) (4) in the drug product formulation.

The overall control strategy for assuring the drug product's identity, strength, purity and quality is deemed adequate based on raw material controls, drug product specification including description, identity and assay of zinc, copper, manganese and selenium; elemental impurities ((b) (4) (b) (4), aluminum content, volume in vial, bacterial endotoxin, particulate matter and sterility. The non-compendial analytical methods were validated per ICH Q2 (R1).

The compatibility of the glass vials at the heel, wall, and shoulder regions was assured via visual inspection, stereomicroscopy, scanning electron microscopy, and ICP-MS.

When used as recommended in the Prescribing Information the drug product appeared to be compatible with common TPNs containing lipids and amino acids such as Kabiven and Clinimix E solutions as demonstrated by the compatibility studies.

Based on the long-term and accelerated stability data of three drug product registration batches assuring the identity, strength, purity and quality, a 24-month of expiration dating period is granted when stored at 20°C- 25°C in the proposed container closure system. (See the **Drug Product** review)

The Office of Process and Facilities (OPF) has made an "Adequate" recommendation for the drug product manufacturing and testing facilities. (See the **Manufacturing Integrated Assessment**)

Manufacturing: Adequate

The drug product is manufactured by American Regent, Inc.; NY (b) (4) (b) (4). The key steps in the drug product manufacturing process include (b) (4) (b) (4)

At appropriate steps during the drug product manufacturing process the following (b) (4) The exhibit batch size is (b) (4) L and the proposed commercial batch size is (b) (4) L. The drug product manufacturing process, in-process controls, drug product release tests and executed batch records were reviewed and deemed satisfactory. (See **Manufacturing Integrated Assessment**)

Microbiology: Adequate

The environmental monitoring at (b) (4) manufacturing process buildings/facilities, component/ equipment (b) (4), (b) (4) of vials and stoppers, container closure integrity, drug product (b) (4) as microbiology related attributes of the drug product specification including bacterial endotoxins and sterility etc., were reviewed and deemed adequate. Based on the satisfactory sterility assurance this NDA was recommended for approval. (See the **Microbiology** review)

Labeling: Adequate

The label/labeling issues have been resolved satisfactorily from the CMC perspective. (See the **Memo to Labeling** review dated May 19, 2020).

Facilities Adequate

The following drug substance and drug product manufacturing, testing and packaging facilities are acceptable.

Facility name and address	Responsibilities and profile code(s)
American Regent, Inc. 5 Ramsey Road, Shirley, New York, United States, 11967	Drug Product Manufacturing, Inspection, Labeling, and Packaging. Chemical and Microbial Testing of Drug Substances and Drug Product
(b) (4)	Drug Substance Manufacturing, Packaging, and Testing of Drug Substances (Selenious Acid, USP and Cupric Sulfate, USP (Pentahydrate))
	Chemical and Microbial Testing of Drug Substances (Selenious Acid, USP and Cupric Sulfate, USP (Pentahydrate))
	Chemical Testing of Drug Substance - Cupric Sulfate, USP (Pentahydrate)
	Drug Substance Manufacturing, Testing, and Packaging for Manganese Sulfate, USP (Monohydrate)
	Drug Substance Manufacturing, Testing, and Packaging for Zinc Sulfate, USP (Heptahydrate)
	Drug Substance Testing, and Packaging (Alternate packager) for Zinc Sulfate, USP (Heptahydrate)
	Chemical and Microbial Testing of Drug Substance - Zinc Sulfate, USP (Heptahydrate)
	Chemical Testing of Drug Product

The Office of Pharmaceutical Manufacturing Assessment has made an overall "Adequate" recommendation for all manufacturing, testing and packaging facilities involved in this application. (see **Manufacturing Integrated Assessment**).

Environmental Assessment: Adequate

The applicant has submitted a claim of categorical exclusion. The categorical exclusion cited at 21 CFR 25.31(a) is appropriate for the submitted application, and a statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is deemed acceptable. (See the **Drug Product** review)

Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
pH	(b) (4)	M	(b) (4)	The vials appear to be compatible with the solution during the shelf life of the drug product None	None
Particulate Matter	(b) (4)	H to M		Particulate matter remained within acceptable range during the stability testing. Low	None
Bioburden	Manufacturing environment and processes	M		Bioburden is controlled in the drug product at release and stability. Low	None
Sterility	Sterilization	M		Sterility is controlled in drug product at release and stability. Low	None

Lifecycle Management Consideration

Drug Product: In eCTD-0019 dated 01/10/2020, the applicant commits to manufacture the first three production batches with each API of at least two different lots that are different from the API lot used for the bridging lot and to provide the results of the risk assessment for elemental impurities for these three production batches in the first annual report. In addition, per Pharm/tox's request, the applicant commits to provide data for (b) (4) from these drug product lots in the first annual report per eCTD-0021 dated 01/14/2020. These data should be evaluated to determine whether routine control of additional elemental impurities as well as (b) (4) is required. The acceptability of the level of (b) (4) should be determined by the Pharm/tox team. In eCTD-0022 dated 2/21/2020, the applicant commits to use a more sensitive analytical procedure (LOQ at 0.25 µg/mL or lower) for (b) (4) in the risk assessment for elemental impurities for the first three commercial lots of drug product and to include the data in the first annual report.

List of Deficiencies for Complete Response: N/A

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
May 26, 2020

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2020.05.27 16:27:58 -04'00'

FDA U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	Type II		(b) (4)	Active	Reviewed by Jeffrey Medwid, 3/5/2019 Adequate	LOA May 23, 2019
	Type II			Active	Reviewed by Friedrich Burnett, 10/15/2019 Adequate	LOA Apr 15, 2019
	Type III			Active	N/A	LOA Dec 11, 2018
	Type III			Active	N/A	LOA Feb 28, 2019
	Type III			Active	N/A	LOA Jan 15, 2019
	Type III			Active	N/A	LOA Jul 24, 2019

B. Other Documents: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	209377	Zinc Sulfate Injection
NDA	209379	Selenious Acid Injection

2. Consults

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received
eCTD-0007 (SDN-12)	09/03/2019
eCTD-0015 (SDN-16)	10/22/2019
eCTD-0024 (SDN-25)	03/20/2020

1.0 PRESCRIBING INFORMATION

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

1) TITLE

TRALEMENT™ (Trace Elements Injection-4, (b) (4)) for intravenous use
(b) (4)

Initial U.S. Approval: 20YY

2) DOSAGE FORMS AND STRENGTHS

(b) (4)

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Drug name [201.57(a)(2)]		
Proprietary name and established name	TRALEMENT™ (Trace Elements Injection-4, USP)	**Unacceptable** The established name "Trace Elements Injection-4, USP", should be replaced with "trace elements injection 4*". (b) (4)" and " (b) (4)" should not be used in the product title. The established name should be in the lower case.
Dosage form, route of administration	Injection, intravenous	**Acceptable**
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval	20YY	**Unacceptable** It should be revised to "2020" if it is approved in 2020 as the first approval for the combination of these four active ingredients.
Dosage Forms and Strengths [201.57(a)(8)]		
Dosage Forms and Strengths in metric system	Dosage form not provided. (b) (4)	**Unacceptable** Dosage form "Injection" should be added. Expression of strength after each element (together with "Each mL contains") is based on the recommendation from the 1/31/2020 PQLC Meeting.
Whether the drug product is scored	N/A	N/A
Package type (for injectable products).* See USP <659> for other package type terms including pharmacy bulk package and imaging bulk package.	Not provided	**Unacceptable** Add "single-dose vial".

*See Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use.

Conclusion: Unsatisfactory

The elements and their corresponding strengths are listed in the order of zinc, copper, manganese, and selenium per USP monograph "Trace Elements Injection". The established name "trace elements injection 4*" follows the USP monograph nomenclature provided in the monograph, as shown below:

> Labeling—Label the Injection to specify that it is to be diluted to the appropriate strength with Sterile Water for Injection or other suitable fluid prior to administration. The label shows by an appropriate number juxtaposed to the official name, the number of trace elements contained in the Injection according to the

following: zinc and copper (2), and then cumulatively, chromium (3), manganese (4), selenium (5), iodine (6), and molybdenum (7). Other combinations are indicated separately by citing the number of trace elements contained in each followed by an asterisk that is repeated with the list of labeled ingredients. Label the Injection for its contents of zinc chloride ($ZnCl_2$), zinc sulfate ($ZnSO_4 \cdot 7H_2O$), cupric chloride ($CuCl_2$), cupric sulfate ($CuSO_4$), chromic chloride ($CrCl_3$), manganese chloride ($MnCl_2$), manganese sulfate ($MnSO_4$), selenious acid (H_2SeO_3), sodium iodide (NaI), and ammonium molybdate [$(NH_4)Mo_7 \cdot 4H_2O$], and for elemental zinc (Zn), copper (Cu), chromium (Cr), manganese (Mn), selenium (Se), iodine (I), and molybdenum (Mo), as appropriate in relation to the ingredients claimed to be present.

The strengths are recommended in mg for zinc and copper and in mcg for manganese and selenium per the recommendation from 1/31/2020 PQLC Meeting. The units of strength also align with the A.S.P.E.N. Position Paper: Recommendations for Changes in Commercially Available Parenteral Multivitamin and Multi–Trace Element Products, which lists the recommended daily amounts in units consistent with the proposed labeling https://onlinelibrary.wiley.com/doi/pdf/10.1177/0884533612446706.

The recommended revisions are shown below:

Title:

TRALEMENT™ (~~Trace Elements Injection 4, USP~~trace elements injection 4*), for intravenous use (b) (4)

Initial U.S. Approval: 2020~~YY~~

DOSAGE FORMS AND STRENGTHS

Injection: (b) (4) 1 mL in a single-dose vial. (b) (4) Each mL contains zinc 3 mg, (b) (4) copper 0.3 mg, manganese 55 mcg, and selenium (b) (4) 60 mcg. (b) (4)

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2: DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

Tralement is supplied as (b) (4) single-dose vials for admixing use only. It is not for direct intravenous infusion. Prior to administration, Tralement must be transferred to a separate parenteral nutrition container and used as an admixture in parenteral nutrition solutions.

The final parenteral nutrition solution is for intravenous infusion into a central or peripheral vein. The choice of a central or peripheral venous route should depend on

the osmolarity of the final infusate. Solutions with osmolarity of 900 mOsm/L or greater must be infused through a central catheter [see Warnings and Precautions (5.2)].

2.2 Preparation and Administration Instructions

- Tralement is not for direct intravenous infusion. Prior to administration, Tralement must be prepared and used as an admixture in parenteral nutrition solutions.
- (b) (4) in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area). The key factor in the preparation is careful aseptic technique to avoid inadvertent touch contamination during mixing of solutions and addition of other nutrients.
- (b) (4) inspect the (b) (4) parenteral nutrition solution containing Tralement for particulate matter before admixing, after admixing, and prior to administration. (b) (4)

2.3 Preparation Instructions for Admixing Using a Parenteral Nutrition Container

- Inspect Tralelment single-dose vial for particulate matter.
- Transfer Tralement to the parenteral nutrition container (b) (4) the admixture of amino acids, dextrose, lipid emulsion (if added), and electrolytes solutions.
- Because additives may be incompatible, evaluate all additions to the parenteral nutrition container for compatibility and stability of the resulting preparation. Consult with pharmacist, if available. (b) (4) additives to the parenteral nutrition container, use aseptic technique.
- Inspect the final parenteral nutrition solution containing Tralement to ensure that:
  - Precipitates have not formed during mixing or addition on additives.
  - The emulsion has not separated, if lipid emulsion has been added. Separation of the emulsion can be visibly identified by a yellowish streaking or the accumulation of yellowish droplets in the admixed emulsion.
  - Discard if any precipitates are observed.

<u>Stability and Storage</u>

- (b) (4)
- Use parenteral nutrition solutions containing Tralement promptly after mixing. Any storage of the admixture should be under refrigeration from 2ºC to 8ºC (36ºF to 46ºF) and limited to (b) (4)

After removal from refrigeration, use promptly and complete the infusion within 24 hours. Discard any remaining admixture.

2.5. Recommended Dosage and Monitoring in Adult and Pediatric Patients

- (b) (4)

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Strengths	(b) (4)	**Unacceptable** The statement for strengths provides the amounts of each element, but fails to indicate that the amounts are for each mL of Tralement. Strengths for zinc and copper should be expressed in mg.
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	• single-dose vial (b) (4)	**Unacceptable** Replace the first two bullets in Stability and Storage of Section 2.3 with "Single-dose vial. Discard unused portion". In section 2.3, add "Cupric ion (b) (4) ascorbic acid; therefore, multivitamin additives should be added to the admixed parenteral nutrition solution shortly before infusion."

Conclusion: Unsatisfactory

Critical information is included, e.g., for admixing use only and not for direct intravenous infusion.

The first two bullets in Stability and Storage of Section 2.3 seem to apply to (b) (4) Since Tralement is a single-dose vial, these two bullets should be revised to "Single-dose vial. Discard unused portion". Data from admixing study support stability and storage of the admixed solution, i.e., the hold time of (b) (4) hours at 2-8°C after admixing and the infusion duration of "within 24 hours". See Drug Product Assessment.

In Section 2.5, expression of strengths should be revised, i.e., mg for Zn and Cu, and mcg for Mn and Se. The recommended revisions are captured on next page.

The following information request was conveyed to the applicant on 3/13/2020.

1. It is well documented in the literature that cupric ion catalyzes degradation of ascorbic acid, which is often included in multivitamins, in total parenteral nutrition (TPN) solutions (e.g., Nutrition 1998, 14 (9), 697-706; J. Am. Chem. Soc. 1967, 89 (16), 4176-4185). As TPN solutions generally include multivitamins and copper, also found in Tralement, please propose statement(s) to include in the labeling to address this issue, including a proper procedure for preparation, storage and administration of TPN admixture solutions containing ascorbic acid to minimize degradation.

In e-CTD0024 dated 3/20/2020, the applicant proposed the following statement in the labeling:

(b) (4)

Conclusion: Unsatisfactory

The applicant's proposed labeling statement missed the point. Oxidation of ascorbic acid occurs more rapidly in the presence of copper. To minimize ascorbic acid degradation in the TPN containing both Tralement and ascorbic acid, one could 1) minimize the oxygen content in TPN admixture (e.g., remove air from TPN bag, use multi-layer bags); 2) minimize the hold time of the admixture containing both Tralement and ascorbic acid. The former option may be more difficult to execute in the clinical setting. The more feasible option is adding ascorbic acid immediately prior to infusion.

The recommended revisions are shown below:

In Section 2.1, replace "900 mOsm/L" with "900 mOsmol/L".

In Section 2.3, add "Cupric ion [redacted] ascorbic acid; therefore, multivitamin additives should be added to the admixed parenteral nutrition solution shortly before infusion".

In Section 2.3 under Stability and Storage, replace the first two bullets with "Single-dose vial. Discard unused portion".

In Section 2.5:

Each mL of Tralement provides zinc [redacted] 3- [redacted] m[redacted]g, copper [redacted] 0.3 [redacted] m[redacted]g, manganese 55 mcg, and selenium [redacted] 60 mcg.

1.2.2 Section 3: DOSAGE FORMS AND STRENGTHS

[redacted]

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Available dosage forms	Injection	**Acceptable**
Strengths: in metric system	(b) (4)	**Unacceptable** Strengths for zinc and copper should be expressed in mg. Do not use bullets for the 4 elements.
Active moiety expression of strength (if applicable)	Active moiety is used for expression of strength.	**Acceptable** Per MAPP 5021.1 Rev.1, an equivalence statement is not needed for Section 3.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Not provided	**Unacceptable** Add "Clear, colorless to slightly blue solution"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
Package type (for injectable products).* Other package type terms include pharmacy bulk package and imaging bulk package.	single-dose	**Acceptable**

*See Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use

Conclusion: **Unsatisfactory**

Per the labeling statement in USP monograph "Trace Elements Injection", the order of the trace elements is zinc, copper, chromium, manganese, selenium, etc. This NDA drug product does not contain chromium. The list of the trace elements in the labeling is recommended to follow the order described in the USP monograph. Based on the consensus reached in the CDER PQLC Meeting held on 1/31/2020 as well as other recently approved NDAs (212121 and 212832), the strength should be placed after each element.

The recommended revisions are shown below:

Injection: 1 mL clear, colorless to slightly blue solution in a single-dose vial. Each (b) (4) mL (b) (4) contains zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg.- (b) (4)

(b) (4)

(b) (4)

1.2.3 Section 11: DESCRIPTION

Tralement™ (Trace Elements Injection-4, USP) is a sterile, non-pyrogenic, clear, and colorless to slightly blue solution, intended for use as a combination of four trace elements and an additive to intravenous solutions for parenteral nutrition.

(b) (4)

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	Tralement™ (Trace Elements Injection-4, USP)	**Unacceptable** Replace "-4" with "4*" for the established name, i.e., trace elements injection 4*, USP. Inclusion of "USP" is acceptable. Use lower case for established name.
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	Injection, intravenous	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) per 21 CFR 201.100(b)(4)	(b) (4)	**Unacceptable** • The strengths in mg for zinc and copper and in mcg for manganese and selenium should be used. • Delete "(b) (4)". Quantitative amounts for Water for Injection and those added to adjust pH are not required for injectable products.
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)] [quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any)]. Not required for oral use, except for colorant For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Inactive ingredients are Water for Injection and sulfuric acid (for pH adjustment)	**Acceptable**
Statement of being sterile [if applicable, 21 CFR 201.57(c)(12)(i)(D)]	"sterile" is included	**Acceptable**
Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	trace elements for parenteral nutrition	**Acceptable**
Chemical name, structural formula [21 CFR 201.57(c)(12)(i)(F)]	(b) (4)	**Unacceptable** The titles of USP monographs for drug substances, which do not include hydrate status, should be used for chemical name. Structural formula of each active ingredient should be provided.
If radioactive, statement of important nuclear characteristics [21 CFR 201.57(c)(12)(i)(G)]	N/A	N/A

Other important chemical or physical properties (such as pKa or pH) [21 CFR 201.57(c)(12)(ii)]	pH 1.5 to 3.5	**Unacceptable** Add the limit of aluminum.
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	N/A No misleading or promotional statement is included.
Package type (for injectable products)*	Not provided	**Unacceptable** Add "single-dose vial"

*See Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use

Conclusion: **Unsatisfactory**

The strength of each element is expressed based on the active moiety. The salt equivalence statement is provided based on the amount of the API in their anhydrous form since the titles of the USP monographs for APIs include no hydrate, e.g., zinc sulfate, instead of zinc sulfate heptahydrate. Where applicable, it is recommended that the hydrate status of the API be included in the structural formula and molecular weight.

Per 21 CFR 201.323, aluminum limit must be included in the container label of all small volume parenteral (SVP) drug products and pharmacy bulk packages (PBPs) used in the preparation of TPN solutions. Even though Prescribing Information (PI) Labeling usually does not include part of the drug product specification, the aluminum limit is recommended to be included in Section 11 since this information is required to be included in the container/carton labels.

This assessor recommended not to include (b) (4) in Section 11 for the following reasons:

(b) (4)

The recommended revisions are shown below:

> Tralement™ (~~T~~trace ~~E~~elements ~~I~~injection ~~-~~4*, USP) is a sterile, non-pyrogenic, clear, and colorless to slightly blue solution, intended for use as a combination of four trace elements and an additive to intravenous solutions for parenteral

nutrition. It contains no preservative.

Each single-dose vial contains 1 mL. *Each mL contains: (b) (4) zinc 3 mg (equivalent to zinc sulfate 7.41 mg), copper 0.3 mg (equivalent to cupric sulfate 0.75 mg), manganese 55 mcg (equivalent to manganese sulfate 151 mcg), selenium 60 mcg (equivalent to selenious acid 98 mcg), and ~~W~~water for ~~I~~injection. (b) (4) Sulfuric acid may be added to adjust pH between 1.5 and 3.5.

(b) (4) Zinc sulfate exists as a heptahydrate, which has a molecular formula of $ZnSO_4 \cdot 7H_2O$ and a molecular weight of 287.54 g/mol.

(b) (4) Cupric sulfate exists as a pentahydrate, which has a molecular formula of $CuSO_4 \cdot 5H_2O$ and a molecular weight of 249.69 g/mol.

Manganese sulfate exists as a monohydrate, which has a molecular formula of manganese sulfate $MnSO_4 \cdot H_2O$ and a molecular weight of 169.02 g/mol.

The molecular formula of selenious acid is H_2SeO_3 and the molecular weight is 128.97 g/mol.

Tralement contains no more than 6,000 mcg/L of aluminum.

The structural formula of each active ingredient should also be provided.

1.2.4 Section 16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Dosage form	Injection	**Acceptable**
Strength of dosage form in metric system	(b) (4)	**Unacceptable** Use the strengths in mg for zinc and copper and in mcg for manganese and selenium. List the elements in the order of zinc, copper, manganese, and selenium per the USP monograph. Do not use bullets for the 4 elements since bullets are recommended for different strengths, not for different active moieties.
Available units (e.g., bottles of 100 tablets)	25 vials per tray	**Acceptable**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number.	(b) (4)	**Unacceptable** The solution description and the NDC number for each vial should be provided. Add "a clear, colorless to slightly blue solution" and the vial NDC 0517-9305-01.
Special handling (e.g., protect from light, refrigerate).	N/A	N/A
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]	**Unacceptable** Add "excursions permitted to 15°C to 30°C (59°F to 86°F)"
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	Vial closure is not made with natural rubber latex	**Acceptable**
Package type (for injectable products).* Other package terms include pharmacy bulk package and imaging bulk package.	single-dose	**Acceptable**

Include information about child-resistant packaging (if manufacturer choose to include)	N/A	N/A

*See Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use

Conclusion: Unsatisfactory

The recommended revisions are shown below:

Tralement™ - (b) (4) is a clear, colorless to slightly blue solution supplied in 1 mL single-dose vials (NDC 0517-9305-01). (b) (4)

Each (b) (4) mL of Tralement~~,~~ contains~~:~~ zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg.

(b) (4)

It is packaged in trays containing 25 vials per tray (NDC 0517-9305-25).
Vial closure is not made with natural rubber latex.

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Store admixed solution at 2ºC to 8ºC (36ºF to 46ºF) *[see Dosage and Administration (2.3)]*.

1.2.5 Other Sections of Labeling

5.3 Aluminum Toxicity

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

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

Conclusion: Unsatisfactory

From CMC perspective, the statement regarding aluminum content, i.e., not more than (b) (4) mcg/kg/day, should be revised to "not more than 0.1 mcg/kg/day" (6 mcg/mL x 1 mL/day/60 kg = 0.1 mcg/kg/day) for the drug product. The recommended revision is shown.

Exposure to aluminum from Tralement is not more than (b) (4) 0.1 mcg/kg/day.

1.2.6 Section 17: PATIENT COUNSELING INFORMATION

AMERICAN
REGENT, INC.
SHIRLEY, NY 11967

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Manufacturer/distributor name [21 CFR 201.1(h)(5)]	AMERICAN REGENT, INC. SHIRLEY, NY 11967	**Unacceptable** Add "Manufactured by".

Conclusion: Unsatisfactory

The recommended revisions are shown below:

Manufactured by
AMERICAN
REGENT, INC.
SHIRLEY, NY 11967

2.0 PATIENT LABELING

Not applicable.

3.0 CARTON AND CONTAINER LABELS

3.1 CONTAINER LABEL

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Tralement™ (Trace Elements Injection-4, USP)	**Unacceptable** Replace "-4" with "4*" for the established name, i.e., trace elements injection 4*, USP. Inclusion of "USP" is acceptable. Font size of the established name is at least half as large as the proprietary name. Use lower case for the established name.
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	Intravenous	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	(b) (4)	**Unacceptable** The strength of each element is not provided. Strength of each element should be provided underneath the established name. If space is permitted, on the side panel, the equivalence statement for the strength of the salts should be provided.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]&	1 mL	**Acceptable**
Name of all inactive ingredients [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]*	Inactive ingredients, i.e., Water for Injection and sulfuric acid, are not provided.	**Acceptable** Per 21 CFR 201.10(i)(2), the information is required for the container label if there is sufficient space. If the label bears a salt equivalence statement, the space may be limited.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided on the top next to NDC number	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not	NDC 0517-9305-01	**Acceptable**

required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]		
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Allocated on the right side	**Acceptable**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Not provided	**Acceptable** It is acceptable that storage statement is not provided due to space limitation per 21 CFR 201.10(i).
Bar code [21CFR 201.25(c)(2)]**	Provided on the right side	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Not provided	**Unacceptable** Add "Recommended Dosage: See Prescribing Information".
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	AMERICAN REGENT, INC. SHIRLEY, NY 11967	**Acceptable**
And others, if space is available	DISCARD UNUSED PORTION Contains no more than 6,000 mcg/L of aluminum.	**Acceptable**
Package type (for injectable products). See USP <659> for other package terms including pharmacy bulk package and imaging bulk package.	SINGLE DOSE VIALS	**Acceptable**

*Except that ingredients added to adjust the pH or to make the drug isotonic may be declared by name and a statement of their effect; and if the vehicle is water for injection it need not be named.

**Requests for an exemption can be made [21 CFR 201.25(d)(ii)(2)]. The bar code requirement does not apply to prescription drug samples [21 CFR 201.25(b)(1)(i)(A)].

Conclusion: **Unsatisfactory**

A CDER PQLC Meeting was held on 1/31/2020 to discuss the following labeling items for this NDA.

a. Interpret USP monograph labeling requirement
b. Recommend an expression of strength for PDP and listing of active ingredients on side panel
c. Discuss use of both mg and mcg in the strength statement

The team reached a consensus for expression of the strength as shown below. The strengths are listed with a leading statement "*Each mL provides:". Each element is listed before the strength. The strengths are expressed as "mg" for Zn and Cu, and as "mcg" for "Mn and Se.

Furthermore, due to space limitation, the committee recommended including the amount of API as the anhydrous salt, instead of the amount for the hydrate, for equivalence statement on the side panel, e.g., zinc sulfate 7.41 mg instead of zinc sulfate heptahydrate 13.2 mg.

The hydrate information for the APIs can be included in the Full Prescribing Information Section 11 Description. Of note, per 21 CFR 201.10(i)(1), if the drug container is too small to bear all labeling information required by FD&C Act 502(e)(1)(A)(ii) and (B), the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

Items 1 and 4 below are based on the outcome of the CDER PQLC Meeting. The following recommendations should be conveyed to the applicant:

1. Replace the established name "Trace Elements Injection-4, USP" with "trace elements injection 4*, USP" and include the strength underneath the established name, as shown below.

   Tralement™
   (trace elements injection 4*, USP)
   *Each mL provides: zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg

2. Add the statement "Recommended Dosage: See full prescribing information"
3. If the space is permitted, replace the statement "Each mL contains: zinc (as sulfate) 3 mg, copper (as sulfate) 0.3 mg, manganese (as sulfate) 55 mcg, selenium (as selenious acid) 60 mcg." on the side panel with "Each mL contains: zinc sulfate 7.41 mg, cupric sulfate 0.75 mg, manganese sulfate 151 mcg, and selenious acid 98 mcg."

3.2 CARTON LABELS

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Tralement™ (Trace Elements Injection-4, USP)	**Unacceptable** Delete "-4" with "4*" for the established name, i.e., trace elements injection 4*, USP. Inclusion of "USP" is acceptable. Font size of the established name is at least half as large as the proprietary name. Use lower case for the established name.
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	Intravenous	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	(b) (4)	**Unacceptable** The strength of each element is not provided. Strength of each element should be provided underneath the established name. The equivalence statement for the strength of the salts (as anhydrous) should be provided.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	25 x 1 mL	**Acceptable**
Name of all inactive ingredients [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Inactive ingredients, i.e., Water for Injection and sulfuric acid, are not provided.	**Unacceptable** Add water for injection and sulfuric acid as inactive ingredients.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC 0517-9305-25	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Allocated on the right side	**Acceptable**
Storage conditions	Store at 20°C to 25°C (68°F to 77°F) [See USP]	**Acceptable**
Bar code [21 CFR 201.25(c)(2)]**	Provided	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	(b) (4)	**Unacceptable** Recommend changing it to "Recommended Dosage: See Prescribing Information" based on DMEPA's management's involvement with the Labeling Workgroup.

"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Not provided	**Acceptable** It is optional for Rx drug.
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	AMERICAN REGENT, INC. SHIRLEY, NY 11967	**Acceptable**
And others, if space is available	DISCARD UNUSED PORTION	**Unacceptable** Add "Contains no more than 6,000 mcg/L of aluminum"
Package type (for injectable products)	SINGLE DOSE VIALS	**Acceptable**

*Except that ingredients added to adjust the pH or to make the drug isotonic may be declared by name and a statement of their effect; and if the vehicle is water for injection it need not be named.

**Requests for an exemption can be made [21 CFR 201.25(d)(ii)(2)]. The bar code requirement does not apply to prescription drug samples [21 CFR 201.25(b)(1)(i)(A)].

Conclusion: Unsatisfactory

The following issues should be addressed:

1. Replace the established name "Trace Elements Injection-4, USP" with "trace elements injection 4*, USP" and include the strength underneath the established name, as shown below

   Tralemt™
   (trace elements injection 4*, USP)
   *Each mL provides: zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg

2. Replace the statement [redacted (b) (4)] with "Each mL contains: zinc sulfate 7.41 mg, cupric sulfate 0.75 mg, manganese sulfate 151 mcg, and selenious acid 98 mcg, and water for injection. Sulfuric acid may be added to adjust pH."
3. Add the statement "Contains no more than 6,000 mcg/L of aluminum"
4. Replace the statement "[redacted (b) (4)]" with "Recommended Dosage: See full prescribing information"

4.0 LIST OF DEFICIENCIES:

A. Regarding PI

a) Highlight Section

1. For the product title, replace the established name "Trace Elements Injection-4, USP" with "trace elements injection 4*" and delete "[redacted (b) (4)] That is, the product title should be "TRALEMENT™ (trace elements injection 4*), for intravenous use".

2. List the year for Initial U.S. Approval as "2020".
3. Revise the DOSAFE FORMS AND STRENGTHS section to "Injection: 1 mL in a single-dose vial. Each mL contains: zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg."

b) Full Prescribing Information

Section 2: DOSAGE AND ADMINISTRATION

4. In Section 2.1, replace "900 mOsm/L" with "900 mOsmol/L".
5. In Section 2.3, add "Cupric ion (b) (4) ascorbic acid; therefore, multivitamin additives should be added to the admixed parenteral nutrition solution shortly before infusion".
6. In Section 2.3 under Stability and Storage, replace the first two bullets with "Single-dose vial. Discard unused portion".
7. In Section 2.5, replace the 1st bullet (b) (4) with "Each mL of Tralement provides zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg."

Section 3: DOSAGE FORMS AND STRENGTHS

8. Add the drug product description "1 mL clear, colorless to slightly blue solution in a single-dose vial".
9. The strengths of zinc and copper should be expressed in "mg" instead of mcg, i.e., zinc 3 mg, copper 0.3 mg. List the elements in the order of zinc, copper, manganese, and selenium per the labeling statement in the USP monograph of Trace Elements Injection. Delete the corresponding salt for the APIs.

Section 5.5: Aluminum Toxicity

10. Revise "not more than (b) (4) mcg/kg/day" to "not more than 0.1 mcg/kg/day".

Section 11: DESCRIPTION

11. Replace the established name "Trace Elements Injection-4, USP" with "trace elements injection 4*, USP".
12. Express the strengths in "mg" for zinc and copper. List the elements in the order of zinc, copper, manganese, and selenium per the USP monograph.
13. Include API salt equivalent statement in the amount of the anhydrous form.
14. Delete (b) (4)" for Water for Injection.
15. Add a structural formula, molecular formula, and molecular weight for each drug substance.
16. Add statements regarding sulfuric acid and pH, package type "single-dose vial", and the limit of aluminum.

Section 16: HOW SUPPLIED/STORAGE AND HANDLING

17. Express the strengths in "mg" for zinc and copper. List the elements in the order of zinc, copper, manganese, and selenium per the USP monograph. Delete the corresponding salt for the APIs.
18. Add the solution description, i.e., a clear, colorless to slightly blue solution, and the NDC number for the vial, i.e., NDC 0517-9305-01.
19. Add "excursions permitted to 15°C to 30°C (59°F to 86°F)" for the storage condition.
20. Add "Store admixed solution at 2° to 8°C (36° to 46°F) *[see Dosage and Administration (2.3)]*."

Section 17: PATIENT COUNSELING INFORMATION

21. Add "Manufactured by" above "AMERICAN REGENT, INC.".

B. Regarding the Container/Carton Labels

22. For the container and carton labels, replace the established name "Trace Elements Injection-4, USP" with "Trace Elements Injection 4*, USP" and include the strength underneath the established name, as shown below.

    Tralement™
    (trace elements injection 4*, USP)
    *Each mL provides: zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg

23. Address the following issues for the container label:
    a. Add the statement "Recommended Dosage: See full prescribing information"
    b. If the space is permitted, replace the statement (b) (4) on the side panel with "Each mL contains: zinc sulfate 7.41 mg, cupric sulfate 0.75 mg, manganese sulfate 151 mcg, and selenious acid 98 mcg."
24. Address the following issues for the carton label:
    a. Replace the statement (b) (4) with "Each mL contains: zinc sulfate 7.41 mg, cupric sulfate 0.75 mg, manganese sulfate 151 mcg, selenious acid 98 mcg, and water for injection. Sulfuric acid may be added to adjust pH."
    b. Add the statement "Contains no more than 6,000 mcg/L of aluminum"
    c. Replace the statement "(b) (4)" with "Recommended Dosage: See full prescribing information"

OVERALL ASSESSMENT:

Issues on the established name, strengths, and lack of product description and NDC number for the vial as well as incomplete inactive ingredients are identified.

Recommendation:

From the ONDP perspective, this application is ***not*** ready for approval in its present form per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Jane Chang, Ph.D.
Senior reviewer
DNDP II/ONDP
04/08/2020

Secondary Assessor Name and Date (and Secondary Summary, as needed):

I agree with Dr. Chang's assessment on the labeling and labels and concur with her recommendation that this application is **not ready for approval** in its present form from the CMC perspective until the deficiencies listed in the **List of Deficiencies** are satisfactorily resolved.

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
DNDP II/ONDP
04/08/2020

Jane Chang

Digitally signed by Jane Chang
Date: 4/14/2020 05:54:54PM
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Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
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GUID: 502d0913000029f9798ca689a802fa55

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 19, 2020

TO: Review #1 of NDA 209376 Quality Assessment - Labeling

FROM: Jane Chang, Ph.D.
Senior Reviewer, OPQ/ONDP/DNDP II

THROUGH Moo-Jhong Rhee, Ph.D.
Chief, Branch 4
OPQ/ONDP/DNDP II

SUBJECT: **Final Recommendation on Labeling/Labels**

SUMMARY

The previous Quality Assessment – Labeling, Assessment Cycle #1 dated 15-Apr-2020, made a recommendation of not ready for approval of this NDA because of labeling deficiencies (see NDA 209376 Labeling R01, Section 4.0). These labeling issues have been satisfactorily resolved based on the revisions made in eCTD-0027 and eCTD-0030.

RECOMMENDATION:

This application is now recommended for **Approval** from the CMC labeling/label perspective.

Assessment Notes

Labeling deficiencies from Quality Assessment were identified in Assessment Cycle #1 dated 15-Apr-2020 (see NDA 209376 Labeling R01, Section 4.0). Subsequently, the following amendments were submitted and assessed.

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received
eCTD-0025 (SDN-27)	04/13/2020
eCTD-0027 (SDN-28)	04/24/2020
eCTD-0030 (SDN-31)	05/15/2020

1. PRESCRIBING INFORMATION

The information provided in eCTD-0030 dated 05/15/2020 is provided below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

1) TITLE

TRALEMENT™ (trace elements injection 4*), for intravenous use

Initial U.S. Approval: 2020

2) DOSAGE FORMS AND STRENGTHS

Injection: 1 mL in a single-dose vial. Each mL contains zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg.

Items	Information Provided in NDA	Assessor's Comment and Recommendations
Drug name [201.57(a)(2)]		
Proprietary name and established name	TRALEMENT™ (trace elements injection 4*)	**Acceptable**
Dosage form, route of administration	Injection, intravenous	**Acceptable**
Controlled drug substance symbol	N/A	N/A
Initial U.S. Approval	2020	**Acceptable** The year that this fixed-combination drug product is approved is used.
Dosage Forms and Strengths [201.57(a)(8)]		
Dosage Forms and Strengths in metric system	Injection. Each mL contains zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg	**Acceptable** The elements are listed in the same order as that in the USP monograph.
Whether the drug product is scored	N/A	N/A
Package type (for injectable products).* See USP <659> for other package type terms including pharmacy bulk package and imaging bulk package.	single-dose	**Acceptable**

*See Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use.

Conclusion: Satisfactory

The information in HIGHLIGHTS OF PRESCRIBING INFORMATION meets the regulatory requirements.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2: DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

Tralement is supplied as a single-dose vial for *admixture use* only. It is *not for direct intravenous infusion*. Prior to administration, Tralement *must be transferred to a separate parenteral nutrition container*, diluted and used as an admixture in parenteral nutrition solution.

The final parenteral nutrition solution is for intravenous infusion into a central or peripheral vein. The choice of a central or peripheral venous route should depend on the osmolarity of the final infusate. Solutions with osmolarity of 900 mOsmol/L or greater must be infused through a central catheter *[see Warnings and Precautions (5.2)]*.

2.2 Preparation and Administration Instructions

- Tralement is not for direct intravenous infusion. Prior to administration, Tralement *must be prepared and used as an admixture* in parenteral nutrition solution.

- Add Tralement to the parenteral nutrition solution in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area). The key factor in the preparation is careful aseptic technique to avoid inadvertent touch contamination during mixing of solutions and addition of other nutrients.

- Inspect the parenteral nutrition solution containing Tralement for particulate matter before admixing, after admixing, and prior to administration.

2.3 Preparation Instructions for Admixing Using a Parenteral Nutrition Container

- Inspect Tralement single-dose vial for particulate matter.

- Transfer Tralement to the parenteral nutrition container after the admixture of amino acids, dextrose, lipid emulsion (if added), and electrolytes solutions is prepared.

- Because additives may be incompatible, evaluate all additions to the parenteral nutrition container for compatibility and stability of the resulting preparation. Consult with pharmacist, if available. For introducing additives to the parenteral nutrition container, use aseptic technique.

- Drug-drug interactions may occur between cupric ion and ascorbic acid. Therefore, multivitamin additives should be added to the admixed parenteral nutrition solution shortly before infusion.

- Inspect the final parenteral nutrition solution containing Tralement to ensure that:

    - Precipitates have not formed during mixing or addition on additives.
    - The emulsion has not separated, if lipid emulsion has been added. Separation of the emulsion can be visibly identified by a yellowish streaking or the accumulation of yellowish droplets in the admixed emulsion.
    - Discard if any precipitates are observed.

Stability and Storage

- Single-dose vial. Discard unused portion.

- Use parenteral nutrition solutions containing Tralement promptly after mixing. Any storage of the admixture should be under refrigeration from 2ºC to 8ºC (36ºF to 46ºF) and limited to a period of no longer than 9 days. After removal from refrigeration, use promptly and complete the infusion within 24 hours. Discard any remaining admixture.

- Protect the parenteral nutrition solution from light.

2.4 Overview of Dosing

Dosing Considerations

- Prior to administration of parenteral nutrition solution containing Tralement, correct severe fluid, electrolyte, and acid-base disorders.

- The dosage of the final parenteral nutrition solution containing Tralement must be based on the concentrations of all components in the solution, the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral intake.
- Monitor fluid and electrolyte status during treatment use of Tralement and adjust the parenteral nutrition solution as needed.

2.5 Recommended Dosage in Adults and Pediatric Patients and Monitoring Considerations

Tralement is a fixed-combination product. Each mL of Tralement provides zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg.

Tralement is recommended only for patients who require supplementation with all four of the individual trace elements (i.e., zinc, copper, manganese and selenium).

Adults and Pediatric Patients Weighing at least 50 kg:

The recommended dosage of Tralement is 1 mL per day added to parenteral nutrition (zinc 3 mg/copper 0.3 mg/manganese 55 mcg/selenium 60 mcg).

Tralement is not recommended for (b) (4) patients (b) (4) who may require a lower dosage of one or more of the individual trace elements.

Pediatric Patients Weighing 10 kg to 49 kg:

The recommended dosage of Tralement added to parenteral nutrition is 0.2 mL to 0.8 mL per day as shown in Table 1 by pediatric weight. (b) (4)

Table 1. (b) (4)

(b) (4)

(b) (4)

Monitoring

- Monitor serum zinc, copper, and selenium concentrations and manganese whole blood concentrations during long-term administration of parenteral nutrition.

- Trace elements concentrations may vary depending on the assay used and the laboratory reference range. The collection, processing, and storage of the blood samples should be performed according to the laboratory's sample requirements for analysis.

    - *Zinc*: In serum, the reported concentration range in healthy adults is 60 to 140 mcg/dL. Zinc concentrations in hemolyzed samples may be falsely elevated due to release of zinc from erythrocytes.
    - *Copper*: In serum, the reported concentration range in healthy adults is 70 to 175 mcg/dL; consider obtaining concentrations of ceruloplasmin along with serum copper.
    - *Manganese*: In whole blood, the lower and upper ends of the reported range in healthy adults are 4 and 16 mcg/L, respectively.
    - *Selenium*: In serum, the reported concentration range in healthy adults is 7 to 19 mcg/dL.

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Strengths	Each mL of Tralement provides zinc 3 mg, copper 0.3 cg, manganese 55 mcg, and selenium 60 mcg.	**Acceptable**
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	• Drug-drug interactions may occur between cupric ion and ascorbic acid. Therefore, multivitamin additives should be added to the admixed parenteral nutrition solution shortly before infusion. • Single-dose vial. Discard unused portion. • Use parenteral nutrition solutions containing Tralement promptly after mixing. Any storage of the admixture should be under refrigeration from 2°C to 8°C (36°F to 46°F) and limited to a period of no longer than 9 days. After removal from refrigeration, use promptly and complete the infusion within 24 hours. Discard any remaining admixture. • Protect the parenteral nutrition solution from light	**Acceptable**

Conclusion: Satisfactory

The admixture study of KABIVEN® and Clinimix E IV admixtures with and without Tralement supports the proposed labeling statement in Section 2.3 of Full Prescribing Information for the admixture storage conditions at 2°C-8°C for up to 9 days (see Quality Drug Product Assessment, Cycle #1 Addendum dated 17-Apr-2020).

The statement in Section 2.5 " (b) (4) seems erroneous because it is inconsistent with the recommended dose for adults weighing at least 50 kg and pediatric patients weighing 10 kg to 49 kg. It seems that the correct statement should be: Tralement is not recommended for (b) (4) patients (b) (4) who may require a lower dosage of one or more of the individual trace elements. This inconsistent statement will be evaluated and addressed by OND.

1.2.2 Section 3: DOSAGE FORMS AND STRENGTHS

Injection: 1 mL clear, colorless to slightly blue solution in a single-dose vial. Each mL contains

zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg.

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Available dosage forms	Injection	**Acceptable**
Strengths: in metric system	zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg	**Acceptable** The elements are listed in the same order as that in the USP monograph.
Active moiety expression of strength (if applicable)	Active moiety is used for expression of strength.	**Acceptable** Per MAPP 5021.1 Rev.1, an equivalence statement is not needed for Section 3.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	clear, colorless to slightly blue solution	**Acceptable**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
Package type (for injectable products).* Other package type terms include pharmacy bulk package and imaging bulk package.	single-dose	**Acceptable**

Conclusion: **Satisfactory**

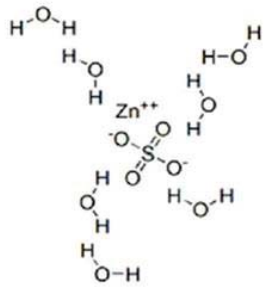
Information in DOSAGE FORMS AND STRENGTHS meets the regulatory requirements.

1.2.3 Section 11: DESCRIPTION

Tralement™ (trace elements injection 4*, USP) is a sterile, non-pyrogenic, clear, and colorless to slightly blue solution, intended for use as a combination of four trace elements and an additive to intravenous solutions for parenteral nutrition. It contains no preservative.

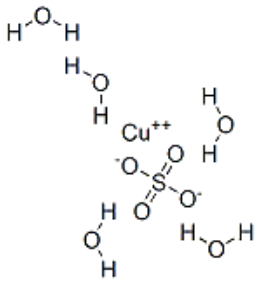
Each single-dose vial contains 1 mL. *Each mL contains zinc 3 mg (equivalent to zinc sulfate 7.41 mg), copper 0.3 mg (equivalent to cupric sulfate 0.75 mg), manganese 55 mcg (equivalent to manganese sulfate 151 mcg), selenium 60 mcg (equivalent to selenious acid 98 mcg), and water for injection. Sulfuric acid may be added to adjust pH between 1.5 and 3.5.

Zinc sulfate exists as a heptahydrate. The structural formula is:



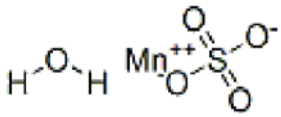
Molecular formula: $ZnSO_4 \cdot 7H_2O$.
Molecular weight: 287.54 g/mol.

Cupric sulfate exists as a pentahydrate. The structural formula is:



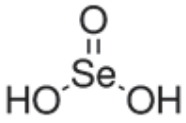
Molecular formula: $CuSO_4 \cdot 5H_2O$.
Molecular weight: 249.69 g/mol.

Manganese sulfate exists as a monohydrate. The structural formula is:



Molecular formula: $MnSO_4 \cdot H_2O$.
Molecular weight: 169.02 g/mol.

The structural formula of selenious acid is:



Molecular formula: H_2SeO_3.
Molecular weight: 128.97 g/mol.

Tralement contains no more than 6,000 mcg/L of aluminum.

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	Tralement™ (trace elements injection 4*, USP)	**Acceptable**
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	Injection, intravenous	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) per 21 CFR 201.100(b)(4)	*Each mL contains zinc 3 mg (equivalent to zinc sulfate 7.41 mg), copper 0.3 mg (equivalent to cupric sulfate 0.75 mg), manganese 55 mcg (equivalent to manganese sulfate 151 mcg), selenium 60 mcg (equivalent to selenious acid 98 mcg).	**Acceptable**
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)] [quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any)]. Not required for oral use, except for colorant. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol.	Inactive ingredients are water for injection and sulfuric acid (for pH adjustment)	**Acceptable**
Statement of being sterile [if applicable, 21 CFR 201.57(c)(12)(i)(D)]	"sterile" is included	**Acceptable**
Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	a combination of four trace elements for parenteral nutrition	**Acceptable**
Chemical name, structural formula [21 CFR 201.57(c)(12)(i)(F)]	Chemical names are provided: Zinc sulfate, Cupric sulfate, Manganese sulfate, Selenious acid. Structural formulas are provided.	**Acceptable**
If radioactive, statement of important nuclear characteristics [21 CFR 201.57(c)(12)(i)(G)]	N/A	N/A
Other important chemical or physical properties (such as pKa or pH) [21 CFR 201.57(c)(12)(ii)]	pH 1.5 to 3.5 Contains no more than 6,000 mcg/L of aluminum.	**Acceptable**
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company	N/A	N/A No misleading or promotional statement is included.

X," "structurally unique molecular entity"		
Package type (for injectable products)*	single-dose vial	**Acceptable**

*See Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use

Conclusion: **Satisfactory**

Information in DESCRIPTION meets the regulatory requirements.

1.2.4 Section 16: HOW SUPPLIED/STORAGE AND HANDLING

Tralement (trace elements injection 4*, USP) is a clear, colorless to slightly blue solution supplied in 1 mL single-dose vials (NDC 0517-9305-01).

*Each mL of Tralement contains zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg.

It is packaged in trays containing 25 vials per tray (NDC 0517-9305-25).

Vial closure is not made with natural rubber latex.

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Store admixed solution at 2ºC to 8ºC (36ºF to 46ºF) *[see Dosage and Administration (2.3)]*.

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Dosage form	injection	**Acceptable**
Strength of dosage form in metric system	zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg	**Acceptable**
Available units (e.g., bottles of 100 tablets)	25 vials per tray	**Acceptable**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number.	clear, colorless to slightly blue solution. NDC 0517-9305-01 for vial and NDC 0517-9305-25 for carton (tray) are provided.	**Acceptable**
Special handling (e.g., protect from light, refrigerate).	N/A	N/A
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Store admixed solution at 2°C to 8°C (36°F to 46°F) [*see Dosage and Administration (2.3)*].	**Acceptable**
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	Vial closure is not made with natural rubber latex.	**Acceptable**
Package type (for injectable products). Other package terms include pharmacy bulk package and imaging bulk package.	single-dose	**Acceptable**
Include information about child-resistant packaging (if manufacturer choose to include)	N/A	N/A

Conclusion: Satisfactory

Information in HOW SUPPLIED/STORAGE AND HANDLING meets the regulatory requirements.

1.2.5 Other Sections of Labeling

5.5 Aluminum Toxicity

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

Exposure to aluminum from Tralement is not more than 0.1 mcg/kg/day. When prescribing Tralement for use in parenteral nutrition containing other small volume parenteral products, the total daily patient exposure to aluminum from the admixture should be considered and maintained at no more than 5 mcg/kg/day *[see Use in Specific Populations (8.4)]*.

Conclusion: Satisfactory

From CMC perspective, the statement regarding aluminum exposure from Tralement, i.e., not more than 0.1 mcg/kg/day, is acceptable. The exposure is calculated as: 6 mcg/mL x 0.2 mL/day/10 kg = 0.12 mcg/kg/day.

1.2.6 Section 17: PATIENT COUNSELING INFORMATION

Manufactured by:

AMERICAN
REGENT, INC.
SHIRLEY, NY 11967

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Manufacturer/distributor name [21 CFR 201.1(h)(5)]	AMERICAN REGENT, INC. SHIRLEY, NY 11967	**Acceptable**

Conclusion: Satisfactory

2.0 PATIENT LABELING

Not applicable.

3.0 CARTON AND CONTAINER LABELS

The following issues were identified in Assessment Cycle #1 dated 15-Apr-2020.

1. For the container and carton labels, replace the established name "Trace Elements Injection-4, USP" with "Trace Elements Injection 4*, USP" and include the strength underneath the established name, as shown below.

Tralement™
(trace elements injection 4*, USP)
*Each mL provides: zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg

2. Address the following issues for the container label:
   a. Add the statement "Recommended Dosage: See full prescribing information"
   b. If the space is permitted, replace the statement [redacted (b) (4)] on the side panel with "Each mL contains: zinc sulfate 7.41 mg, cupric sulfate 0.75 mg, manganese sulfate 151 mcg, and selenious acid 98 mcg."
3. Address the following issues for the carton label:
   a. Replace the statement [redacted (b) (4)] with "Each mL contains: zinc sulfate 7.41 mg, cupric sulfate 0.75 mg, manganese sulfate 151 mcg, selenious acid 98 mcg, and water for injection. Sulfuric acid may be added to adjust pH."
   b. Add the statement "Contains no more than 6,000 mcg/L of aluminum"
   c. Replace the statement "[redacted (b) (4)]" with "Recommended Dosage: See full prescribing information"

3.1 CONTAINER LABEL

The container label provided in eCTD-0025 dated 04/13/2020 is shown below.

Conclusion: **Unsatisfactory**

The following recommendations for container label were conveyed to the applicant on 4/20/2020:

1. Express the proprietary name, established name, and strength as following:

   Tralement™
   (trace elements injection 4*, USP)
   *Each mL provides: zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg

   Based on FDA internal multidiscipline discussions, we recommend using "mg" for the strength of zinc and copper and "mcg" for the strength of manganese and selenium. The recommended strength units are consistent with those of the approved Zinc Sulfate Injection (NDA 209377) and Selenious Acid Injection (NDA 209379).

   Your container label submitted on 4/13/2020, (b) (4) , is not acceptable. The chemical name of each element, (b) (4) , should be used to avoid medical errors. ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations mentions "To avoid confusion, do not abbreviate drug names when communicating medical information." If space is an issue, you may consider eliminating other information such as the statement for active ingredients on the side panel.

   The elements must be listed in the same order as that of the USP monograph, i.e., zinc, copper, manganese, and selenium.

2. Provide the amounts of zinc sulfate and copper sulfate in "mg", instead of "mcg". List the active ingredients in the same order as that of the USP monograph. On the container label, if space is permitted, revise the statement for active ingredients to "Each mL contains: zinc sulfate 7.41 mg, cupric sulfate 0.75 mg, manganese sulfate 151 mcg, and selenious acid 98 mcg."
3. Indicate the location of lot number and expiration date.

In eCTD-0027 dated 4/24/2020, the applicant provided the following revised label:

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Tralement™ (trace elements injection 4*, USP)	**Acceptable** Font size of the established name is at least half as large as the proprietary name.
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	Intravenous	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Strength: *Each mL provides: zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg	**Acceptable** Per 21 CFR 201.10(i)(1), it is acceptable that equivalence statement is omitted due to space limitation.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)][&]	1 mL	**Acceptable**
Name of all inactive ingredients [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Not provided.	**Acceptable** Per 21 CFR 201.10(i)(1), if the drug container is too small to bear all labeling information required by FD&C Act 502(e)(1)(A)(ii) and (B), the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug. Therefore, due to limited space, the inactive ingredients do not need to be included.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided on the top next to NDC number	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC 0517-9305-01	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	The applicant stated that "LOT" and "EXP" as well as the actual lot number and expiration date, will be imprinted on the very far right side of the label, following the bar code. See Section 1.14.1.2.	**Acceptable**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Not provided	**Acceptable** It is acceptable that storage statement is not provided due to space limitation per 21 CFR 201.10(i)(1).
Bar code [21CFR 201.25(c)(2)]	Provided on the right side	**Acceptable**

Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Not provided	**Acceptable** The statement "Recommended Dosage: See Prescribing Information" can be omitted for the container label due to space limitation per 21 CFR 201.10(i)(1).
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	AMERICAN REGENT, INC. SHIRLEY, NY 11967	**Acceptable**
And others, if space is available	Discard Unused Portion For intravenous use after dilution and admixing. Contains no more than 6,000 mcg/L of aluminum.	**Acceptable**
Package type (for injectable products). See USP <659> for other package terms including pharmacy bulk package and imaging bulk package.	Single-Dose Vial	**Acceptable**

Conclusion: Satisfactory

The issues identified for container label in Assessment Cycle #1 dated 15-Apr-2020 and 4/20/2020 Information Request have been addressed. The information on the container label meets the regulatory requirements.

3.2 CARTON LABEL

The information provided in eCTD-0025 dated 04/13/2020 is shown below.

Conclusion: Unsatisfactory

See Item 1 recommendation provided on page 15 for expression of proprietary name, established name, strength and the elements order. In addition, the following recommendations were conveyed to the applicant on 4/20/2020:

1. Provide the amount of zinc sulfate and copper sulfate in "mg", instead of "mcg". List the active ingredients in the same order as that of the USP monograph. Revise the statement for ingredients to "Each mL contains: zinc sulfate 7.41 mg, cupric sulfate 0.75 mg, manganese sulfate 151 mcg, selenious acid 98 mcg, and water for injection."

In eCTD-0027 dated 4/24/2020, the applicant provided the following revised label:

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Tralement™ (trace elements injection 4*, USP)	**Acceptable** Font size of the established name is at least half as large as the proprietary name.
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	Intravenous	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21	Each mL provides: zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg.	**Acceptable**

CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Each mL contains: zinc sulfate 7.41 mg, cupric sulfate 0.75 mg, manganese sulfate 151 mcg, selenious acid 98 mcg, and water for injection.	
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	25 x 1 mL	**Acceptable**
Name of all inactive ingredients [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Inactive ingredients, i.e., water for injection and sulfuric acid, are included.	**Acceptable**
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC 0517-9305-25	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Allocated on the right side	**Acceptable**
Storage conditions	Store at 20°C to 25°C (68° to 77°F) [See USP]	**Acceptable**
Bar code [21 CFR 201.25(c)(2)]**	Provided	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Recommended Dosage: See Prescribing Information	**Acceptable**
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Not provided	**Acceptable** It is optional for Rx drug.
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	AMERICAN REGENT, INC. SHIRLEY, NY 11967	**Acceptable**
And others, if space is available	Discard Unused Portion	**Acceptable** Per 21 CFR 201.323, the statement of maximum level of aluminum present at the expiry is required for immediate container label of all small volume parenteral drug products and pharmacy bulk packages used in the preparation of TPN solution. There is no requirement for the Aluminum limit statement on the carton label.
Package type (for injectable products)	Single-Dose Vials	**Acceptable**

Conclusion: Satisfactory

The issues identified for carton label in Assessment Cycle #1 dated 15-Apr-2020 and 4/20/2020 Information Request have been addressed. The information on the carton label meets the regulatory requirements.

Jane Chang

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Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 5/19/2020 12:53:36PM
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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	209376
Assessment Cycle Number	1
Drug Product Name/ Strength	Trace Elements Injection-4, USP (b) (4) [redacted] Tralement
Route of Administration	IV infusion
Applicant Name	American Regent, Inc.
Therapeutic Classification/ OND Division	Division of Gastroenterology and Inborn Errors Products
Manufacturing Site	American Regent, Inc., 5 Ramsey Rd, Shirley, NY 11967
Method of Sterilization	(b) (4) [redacted]

Assessment Recommendation: **Adequate**

Assessment Summary: Recommended

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0007 (12) ORIG-1	**09/03/2019**
0014 (15) ORIG1/Labeling/SPL Draft	**09/13/2019**
0016 (17) Amendment/Quality IR Response	**11/20/2019**
0025 (27) Amendment	**4/13/2020**

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: N/A

Concise Description of Outstanding Issues: N/A

Supporting Documents:

- **DMF** (b) (4) [redacted] **for** (b) (4) [redacted]
  - (b) (4) [redacted] **mic33.doc dated 04/25/2017 (adequate)**

S DRUG SUBSTANCE

No review was conducted on the drug substance as the drug substance is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of the drug product –** Sterile, simple solution of 1 mL packaged in 2 mL (b) (4) glass vials closed with (b) (4) stoppers and sealed with (b) (4) tops.
- **Drug product composition –**
(Section 3.2.P.1 Description and Composition of Drug Product p.2-3)

Ingredient/Quality	Function	% w/v	Quantity/1 mL*
Zinc Sulfate heptahydrate / USP	API	(b) (4)	
Cupric Sulfate pentahydrate / USP	API		
Manganese Sulfate monohydrate / USP	API		
Selenious Acid, USP	API		
Sulfuric Acid, USP	pH adjuster		
WFI, USP	(b) (4)		

* A (b) (4) mL target fill volume has been established based on USP <1511> requirements for mobile liquids

- **Description of container closure system –**
(Section 3.2.P.1 Description and Composition of Drug Product, p.5)

Primary Package Component	Description	Manufacturer
Vial	(b) (4)	
Stopper		
Seal		

Assessment: Adequate
The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

(Section 3.2.P.2 Container-Closure-Integrity-Test-Microbial)

CCIT validation by microbial ingress was performed using the [redacted] (b) (4) stoppers and 5 mL tubular glass vials. The test was performed using TSB media (lot #RD13-009).

Test Method

Vials were submerged in a culture of *B.diminuta* $\geq 10^6$ cfu/mL. For each study date, two test vials were inoculated with 0.1 mL (10-100 cfu) of challenge organism and growth observed in both vials. Viable plate counts were also performed in duplicate on the aliquot used for the growth promotion studies. Twenty samples, two positive, and two negative controls were tested initially and after 1, 2, 3, 4, and 5 years. Positive controls were prepared by inserting a capillary tubing into a 16-gauge needle which was inserted into the rubber stopper prior to the entire stoppered vial being submerged in test culture.

Prior to testing, test vials filled with TSB were exposed to a [redacted] (b) (4) process [redacted] (b) (4) Once submerged in test culture, the vials in suspension were transferred to a vacuum vessel where a vacuum of 15 inHg was applied for 30 min. Containers were removed and incubated at 30-35°C for 7 days.

Acceptance criteria

- No growth in test vials
- Growth promotion test results are positive
- Positive controls show growth growth; negative show no growth
- Test culture suspension concentration is $\geq 10^6$ cfu/mL

Results summary

Data provided show that all established acceptance criteria were met for the microbial ingress study. All positive controls were positive, and all negative controls were negative. Results are summarized in the table below:

Test Date	Results Tested/Positive	Concentration of Challenge Organism (cfu/mL)
08/05/2013	20/0	2.5×10^9
08/04/2014		9.0×10^8
08/03/2015		7.9×10^7
08/01/2016		1.9×10^9
08/014/2017		1.3×10^9
08/31/2018		6.7×10^7

The following deficiency was issued in the Agency's Information Request dated 11/4/2019:

Regarding the container closure integrity testing (container-closure-integrity-test-microbial.pdf), it is noted that the microbial ingress test was performed with a 5 mL tubular glass vial and 13 mm rubber stopper, while the proposed container closure

system is a 2 mL tubular glass vial and 13 mm rubber stopper. Please provide a comparison of the inner neck diameter of the 5 mL vial used for the container closure integrity test and the 2 mL vial proposed for the commercial drug product. If the inner neck diameters of the subject drug product vials are not the same as or bracketed by those used in the study, please provide results of container closure integrity testing performed using the proposed drug product stoppers and vials with the same inner neck diameter specification as those proposed for production.

In their response dated 11/20/2019, the applicant stated that the neck sizes for the 5 mL vial used for CCIT and the 2 mL vials proposed for the subject drug product are identical (6.86-7.24 mm for both). In addition, the stopper proposed for the drug product is identical to the stopper used for CCIT.

Assessment: Adequate

The integrity of the proposed container closure system was adequately validated.

Antimicrobial Effectiveness Testing – N/A

P.3 MANUFACTURE

P.3.1 MANUFACTURERS

(b) (4)

12 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

P.8 STABILITY

P.8.1 STABILITY SUMMARY AND CONCLUSION

(Section 3.2.P.8.1 Stability Summary and Conclusion)

The stability protocol includes accelerated, intermediate, and long-term (labeled) stability tests for bacterial endotoxins and sterility; the acceptance criteria for these tests were the same as the criteria at release. The testing schedule in the stability protocol is as follows:

Stability storage conditions:

- Accelerated: 40°C ± 2°C / 75% RH ± 5% RH (batches RD15-013, RD16-001, RD16-007); testing 0, 1, 3, 6 months
- Intermediate: 30°C ± 2°C / 65% RH ± 5% RH (batch RD16-007 only); testing 0, 3, 6, 9, and 12 months
- Long-term: 25°C ± 2°C / 60% RH ± 5% RH (batches RD15-013, RD16-001, RD16-007); testing 0, 3, 6, 9, 12, 18, and 24 months

Stability studies have been completed for three exhibit batches of Trace Elements Injection-4, USP (RD15-013, RD16-001, RD16-007. Data provided for sterility and bacterial endotoxin testing show that all samples comply with established specifications throughout the duration of each storage condition.

Proposed expiry: 24 months

Assessment: Adequate

The applicant has proposed an acceptable expiration period for the subject drug product.

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

(Section 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment)

The product stability specification includes the following microbiological tests:

Test	Test method	Specification at release
Sterility	USP<71>	Sterile
Endotoxins	USP<85>	(b) (4) EU/mL

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 25°C / 60% RH

First three commercial and annual batch testing intervals
Sterility: 0, 12, 24 months
BET: 0, 24 months

(b) (4)

Post Approval Stability Commitment
The applicant commits to placing the first three commercial lots of the subject drug product into their long-term stability program as noted above. Thereafter, on an annual basis, a minimum of one production lot will be added to the stability program.

Assessment: Adequate

The post-approval stability protocol and stability commitment are adequate to assure the maintenance of microbiological quality over the proposed shelf-life of the subject drug product.

P.8.3 STABILITY DATA

(Section 3.2.P.8.3 Stability Data)

Accelerated, intermediate, and long-term stability studies performed on exhibit batches RD15-013, RD16-001, RD16-007 are complete and data are included. Six-month accelerated and long-term stability data for bridging batch RD18-007 are also included. Samples analyzed for microbiology comply with the specifications for bacterial endotoxins and sterility.

Assessment: Adequate

The stability data provided support the maintenance of microbiological quality for the subject drug product [redacted] (b) (4)

R REGIONAL INFORMATION

Executed Batch Records

Executed lot #(s): RD15-013, RD16-001, RD16-007, RD18-007

Assessment: *Adequate*

The batch records confirm that validated [redacted] (b) (4) processes were used for the manufacture of the exhibit batches.

Comparability Protocols – No CP was included in the application.

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

Post-dilution/constitution hold time
(Section 1.14.1.3 Draft Labeling Text, Section 3.2.P.2 admixture-study-antimicrobial-effectiveness)

Container: 2 mL glass vial
Route of Administration: IV infusion

While each vial is labeled as single-dose, Multi-Element is a pharmacy bulk package. It is to be stored at 20-25°C with excursions permitted to 15-30°C. The label specifies that [redacted] (b) (4)

(b) (4)

Reduced inoculation antimicrobial effectiveness studies were performed for Trace Elements Injection-4, USP in parenteral nutrition admixtures of Kabiven® and Clinimax (Section 3.2.P.2).

For each study, 1 mL of drug product is injected into the admixture bag and mixed. The bulk dilution is split into 10 mL aliquots, which are challenged with appropriate compendial microorganisms at low inoculum levels (< 100 cfu/mL per aliquot) for up to 72 hours at 2-8°C and 20-25°C storage conditions.

Non-product-containing positive controls were prepared, inoculated, and plated similarly to the test articles (1 mL of each aliquot onto TSA plates for bacteria or SDA plates for fungi). TSA plates were incubated at 30-35°C for three days, SDA plates at 20-25°C for five days, and recovery was calculated. The recovery from the test article must be at least 50% to demonstrate that the recovery method is suitable.

Study data provided showed that both Clinimax E and Kabiven® admixture solutions with and without 1 mL of Trace Elements Injection-4, USP stored at 2-8°C for up to 72 hours met the acceptance criteria of "no growth," which is interpreted from recovery counts of not more than 0.5 log increase from the calculated inoculum concentration.

Study data provided also showed that the Kabiven® admixture stored for 24, 48, and 72 hours at 20-25°C did not meet the acceptance criteria with reported log recoveries of *C.albicans* of more than 0.5 log increases. The Clinimax E admixture solution did meet acceptance criteria at both 3-8°C and 20-25°C for 72 hours.

Overall the results support the package insert statements, "(b) (4)

Update from 04/13/2020 Submission

In their 04/13/2020 submission, the applicant changed their labeling regarding storage time to say the following:

"Use parenteral nutrition solutions containing Tralement promptly after mixing. Any storage of the admixture should be under refrigeration from 2ºC to 8ºC (36ºF to 46ºF) and limited to a period of no longer than 9 days. After removal from refrigeration, use

promptly and complete the infusion within 24 hours. Discard any remaining admixture." (Section 1.14.1.3 Draft Labeling Text)

In order to support the change from storage of the admixture for (b) (4) hours to 9 days at 2-8°C, a new 14-day admixture study with both Clinimax E and Kabiven® admixture solutions was performed and included in the 04/13/2020 submission. The initial admixture study was performed for 3 days. The current study included a reduced inoculation antimicrobial effectiveness study to determine whether or not there would be adventitious microbial contamination growth during the preparation and storage of the Tralement admixtures.

The method of testing was the same as described above using compendial microorganisms. Of note, the inoculum concentration of C.albicans exceeded the upper limit of 100 cfu/mL (120 cfu/mL), with a reported log cfu recovery of 2.1. There was no impact on the study as the log cfu recoveries were accurately enumerated at each time point. The protocol's acceptance criteria is "no growth" which is defined as NMT 0.5 log increases form the calculated inoculum concentration. Samples were tested at 0, 5, 7, 10, and 14 days after incubation at 2-8°C.

Study data provided show that KABIVEN® and Clinimix E IV admixtures with and without Tralement stored for up to 14 days at 2-8°C meeting the acceptance criteria of "no growth." The study data support the current product admixture labeling storage conditions of up to 9 days at 2-8°C.

Assessment: Adequate

The package insert provides adequate instructions for storage of the subject drug product to assure the microbiological quality of the subject drug product during administration.

Primary Microbiology Assessor Name and Date: Bethanie L. Lee, Ph.D. 04/15/2020

Secondary Assessor Name and Date (and Secondary Summary, as needed): Jesse Wells, Ph.D. 04/15/2020

Jesse Wells

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Bethanie Lee

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