CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

209376Orig1s002

Trade Name:	MULTRYS
Generic or Proper Name:	(trace elements injection 4)
Sponsor:	American Regent Inc.
Approval Date:	June 30, 2021
Indication:	MULTRYS is a combination of trace elements (zinc sulfate, cupric sulfate, manganese sulfate, and selenious acid) indicated in neonatal and pediatric patients weighing less than 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

209376Orig1s002

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	
Product Quality Review(s)	
Non-Clinical Review(s)	X
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	X
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

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209376Orig1s002

APPROVAL LETTER

NDA 209376/S-002

SUPPLEMENT APPROVAL

American Regent, Inc.
Attention: Elizabeth Ernst,
Global Executive Director of Regulatory Affairs
6610 New Albany Road East
New Albany, OH 143054

Dear Ms. Ernst,

Please refer to your supplemental new drug application (sNDA) dated and received on December 11, 2021, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Multrys (trace elements injection 4*).

This Prior Approval supplemental new drug application provides for the addition of a new strength (1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with minor editorial revisions reflected in the enclosed labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling or carton and container labeling submitted on **June 2, 2021**, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 209376/S-002**." Approval of this submission by FDA is not required before the labeling is used.

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

We have received your submission dated December 11, 2020, containing the final report for the following postmarketing requirement listed in the July 2, 2020, approval letter.

3877-2 To develop a weight-appropriate formulation for pediatric patients weighing less than 10 kilograms.

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there is a postmarketing requirement listed in the July 2, 2020, approval letter that is still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.[3]

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Thao Vu, Regulatory Project Manager, at (240) 402-2690.

Sincerely,

{See appended electronic signature page}

Frank A. Anania, M.D., FACP, AGAF, FAASLD
Deputy Director
Division of Hepatology and Nutrition
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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

/s/

FRANK A ANANIA
06/30/2021 09:19:06 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209376Orig1s002

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MULTRYS™ safely and effectively. See full prescribing information for MULTRYS™.

MULTRYS™ (trace elements injection 4*), for intravenous use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------

Multrys is a combination of trace elements (zinc sulfate, cupric sulfate, manganese sulfate, and selenious acid) indicated in neonatal and pediatric patients weighing less than 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. (1)

----------DOSAGE AND ADMINISTRATION----------

- *Single-dose vial, for admixture use only.* (2.1)
- See full prescribing information for information on preparation, administration and general dosing considerations. (2.1, 2.2, 2.3, 2.4)

Recommended Dosage

- Each mL of Multrys provides zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg. (2.5)
- Multrys is recommended only for pediatric patients who require supplementation with all four of the individual trace elements (i.e., zinc, copper, manganese, and selenium) to meet daily requirements. (2.5)
- *Pediatric Patients 0.4 kg to 0.59 kg*: The total recommended dosage of Multrys is 0.2 mL **every other day**. Daily supplementation of Zinc Sulfate, Cupric Chloride and Selenious Acid will be needed to meet daily requirements. (2 5)
- *Pediatric Patients 0.6 kg to 10 kg*: The recommended dosage of Multrys is 0.3 mL/kg/day rounded to the nearest 0.1 mL for up to a maximum of 1 mL per day. The recommended volume of Multrys to be added to parenteral nutrition ranges from 0.2 mL per day to 1 mL per day based on body weight. (2 5)
- Multrys is not recommended for patients who may require a lower dosage of one or more of the individual trace elements. (2.5)
- Monitor trace element concentrations in blood during long-term administration of parenteral nutrition. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: Each mL contains zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg in a 1 mL, single-dose vial. (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to zinc or copper (4, 5.7)

----------WARNINGS AND PRECAUTIONS----------

- Pulmonary Embolism due to Pulmonary Vascular Precipitates: If signs of pulmonary distress occur, stop the infusion and initiate a medical evaluation. (5.1)
- Vein Damage and Thrombosis: Solutions with osmolarity of 900 mOsmol/L or more must be infused through a central catheter. (2.1, 5.2)
- Neurologic Toxicity with Manganese: Monitor for clinical signs and symptoms of neurotoxicity, whole blood manganese concentrations, and liver function tests in patients receiving long-term Multrys. Discontinue Multrys and consider brain magnetic resonance imaging (MRI) if toxicity is suspected. (5.3)
- Hepatic Accumulation of Copper and Manganese: Assess for development of hepatic accumulation. Monitor concentrations of copper and manganese in patients with cholestasis or cirrhosis receiving Multrys long-term. (5.4)
- Aluminum Toxicity: Increased risk in patients with renal impairment, including preterm infants. (5.5)
- Monitoring and Laboratory Tests: Monitor zinc, copper, and selenium serum concentrations, whole blood manganese concentration, fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, blood count, and coagulation parameters. (5.6, 2.4)
- Hypersensitivity Reactions with Zinc and Copper: If reactions occur, discontinue Multrys and initiate appropriate medical treatment. (5.7)

To report SUSPECTED ADVERSE REACTIONS, contact American Regent, Inc. at 1-800-734-9236 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Multrys is indicated in neonatal and pediatric patients weighing less than 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

Multrys is supplied as a single-dose vial for *admixture use* only. Prior to administration, Multrys *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

- Multrys is for *admixture use* only. Prior to administration, Multrys *must be prepared and used as an admixture* in parenteral nutrition solution.

- Add Multrys 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 Multrys for particulate matter before admixing, after admixing, and prior to administration.

2.3 Preparation Instructions for Admixing Using a Parenteral Nutrition Container

- Inspect Multrys single-dose vial for particulate matter.

- Transfer Multrys to the parenteral nutrition container after the admixture of amino acids, dextrose, lipid emulsion (if added), and electrolyte 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 a pharmacist, if available. For introducing additives to the parenteral nutrition container, use aseptic technique.

- An interaction 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 Multrys to ensure that:

    - Precipitates have not formed during mixing or addition of 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 any unused portion.

- Penetrate vial closure only one time with a suitable sterile transfer device or dispensing set that allows measured dispensing of the contents.

- Transfer Multrys to the parenteral nutrition container promptly after removal from the vial. Discard any remaining drug.

- Use parenteral nutrition solutions containing Multrys 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

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

- The dosage of the final parenteral nutrition solution containing Multrys 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 Multrys and adjust the parenteral nutrition solution as needed.

2.5 Recommended Dosage in Pediatric Patients and Monitoring Considerations

Multrys is a fixed-combination product. Each mL of Multrys provides zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg.

Recommended Dosage for Pediatric Patients Weighing 0.4 kg to 0.59 kg

- The total recommended dosage of Multrys is 0.2 mL **every other day.**

- Daily supplementation of Zinc, Copper, and Selenium will be needed to meet daily requirements (See Table 2 below).

Recommended Dosage for Pediatric Patients Weighing 0.6 kg to less than 10 kg

- The recommended dosage of Multrys is 0.3 mL/kg/day rounded to nearest 0.1 mL for up to a maximum of 1 mL per day.

- The recommended volume of Multrys to be added to parenteral nutrition ranges from 0.2 mL per day to 1 mL per day based on body weight, see Table 1 below.

Table 1. Recommended Daily Volume of Multrys and Corresponding Amount of Each Trace Element (mcg)

Body Weight	Recommended Daily Volume	Amount of Trace Element Provided by the Corresponding Multrys Volume			
		Zinc mcg	Copper mcg	Manganese mcg	Selenium mcg
0.6 kg to 0.8 kg	**0.2 mL**	200	12	0.6	1.2
0.9 kg to 1.1 kg	**0.3 mL**	300	18	0.9	1.8
1.2 kg to 1.4 kg	**0.4 mL**	400	24	1.2	2.4
1.5 kg to 1.7 kg	**0.5 mL**	500	30	1.5	3
1.8 kg to 2 kg	**0.6 mL**	600	36	1.8	3.6
2.1 kg to 2.3 kg	**0.7 mL**	700	42	2.1	4.2
2.4 kg to 2.6 kg	**0.8 mL**	800	48	2.4	4.8
2.7 kg to 2.9 kg	**0.9 mL**	900	54	2.7	5.4
3 kg to 9.9 kg	**1 mL**	1,000	60	3	6

Additional Trace Element Supplementation with Multrys

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

- To determine the additional amount of supplementation that is needed, compare the calculated daily recommended dosage based on the body weight of the patient to the amount of each trace element provided by Multrys and enteral nutrition sources.

Table 2: Daily Requirement for Trace Element Supplementation for Pediatric Patients

Trace Element	Patient Weight (kg)	Daily Requirement*
Zinc	Less than 3 kg	400 mcg/kg/day
	3 kg to 5 kg	250 mcg/kg/day
	5 to 10 kg	100 mcg/kg/day
Copper	-	20 mcg/kg/day
Selenium	-	2 mcg/kg/day
Manganese**	-	1 mcg/kg/day

*Multrys is not recommended for pediatric patients who may require a lower dosage of one or more of these individual trace elements.

**Avoid additional manganese supplementation with Multrys use. Accumulation of manganese in the brain can occur with long-term administration with higher than the recommended dosage of 1 mcg/kg/day *[see Warnings and Precautions (5.3)]*.

For pediatric patients weighing less than 3 kg, Multrys does not provide the recommended daily dosage of zinc.

- Zinc: For patients weighing less than 3 kg, add Zinc Sulfate to provide total daily recommended dose of 400 mcg/kg/day using parenteral and/or enteral routes of administration.

For pediatric patients weighing 0.4 kg to 0.59 kg and 4 kg to 9.9 kg, Multrys does not provide the recommended daily dosage of copper or selenium.

- Copper: For patients weighing 0.4 to 0.59 kg or 4 kg to 9.9 kg, add Cupric Chloride to provide total daily recommended dose of 20 mcg/kg/day using parenteral and/or enteral routes of administration.

- Selenium: For patients weighing 0.4 to 0.59 kg or 4 kg to 9.9 kg, add Selenious Acid to provide total daily recommended dose of 2 mcg/kg/day using parenteral and/or enteral routes of administration.

Monitoring

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

- Trace element 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.

3 DOSAGE FORMS AND STRENGTHS

Injection: Each mL of Multrys contains zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg in a clear, colorless to slightly blue solution, single-dose vial.

4 CONTRAINDICATIONS

Multrys is contraindicated in patients with hypersensitivity to zinc or copper *[see Warnings and Precautions (5.7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Pulmonary Embolism due to Pulmonary Vascular Precipitates

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

5.2 Vein Damage and Thrombosis

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

5.3 Neurologic Toxicity with Manganese

Pediatric patients on long-term parenteral nutrition receiving manganese at higher than recommended dosages and pediatric patients with cholestatic liver disease have experienced manganese accumulation in the basal ganglia. Some adult patients with brain MRI findings reportedly experienced neuropsychiatric symptoms, including changes in mood or memory, seizures and/or parkinsonian-like tremors, dysarthria, mask-face, and halting gait. Some pediatric patients experienced dystonic movements or seizures. Brain MRI findings and clinical symptoms have also been observed in patients who received manganese at or below the recommended dosage and with normal blood manganese concentrations. Regression of symptoms and brain MRI findings have occurred over weeks to months following discontinuation of manganese in most patients but have not always completely resolved.

Monitor patients receiving long-term parenteral nutrition solutions containing Multrys for neurologic signs and symptoms and routinely monitor whole blood manganese concentrations and liver function tests. In case of suspected manganese toxicity or new neuro-psychiatric manifestations, temporarily discontinue Multrys, check manganese whole blood concentrations, and consider brain MRI evaluation.

Monitor patients receiving Multrys for cholestasis or other biliary liver disease. Consider individual trace element products as an alternative to Multrys in patients with hepatobiliary disease *[see Warnings and Precautions (5.4)]*.

5.4 Hepatic Accumulation of Copper and Manganese

Copper is primarily eliminated in the bile and excretion is decreased in patients with cholestasis and/or cirrhosis. Hepatic accumulation of copper and manganese have been reported in autopsies of patients receiving long-term parenteral nutrition containing copper and manganese at dosages higher than recommended.

Patients with cholestasis and/or cirrhosis receiving parenteral nutrition are at increased risk of manganese brain deposition and neurotoxicity *[see Warnings and Precautions (5.3)]*.

Administration of copper to patients with cholestasis and/or cirrhosis may cause hepatic accumulation of copper. Administration of copper to patients with Wilson disease, an inborn error of copper metabolism with a defect in hepatocellular copper transport, may cause both increased hepatic accumulation of copper and aggravation of the underlying hepatocellular degeneration.

If a patient develops signs or symptoms of hepatobiliary disease during the use of Multrys, obtain serum concentrations of copper and ceruloplasmin as well as manganese whole blood concentrations; consider using individual trace element products in these patients *[see Use in Specific Populations (8.6)]*.

5.5 Aluminum Toxicity

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

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

Exposure to aluminum from Multrys is not more than 0.45 mcg/kg/day. When prescribing Multrys 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.

5.6 Monitoring and Laboratory Tests

Monitor zinc, copper, and selenium serum concentrations, manganese whole blood concentration, fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, blood count, and coagulation parameters during use of parenteral nutrition containing Multrys *[see Dosage and Administration (2.4)]*.

5.7 Hypersensitivity Reactions with Zinc and Copper

Postmarket safety reporting has identified zinc hypersensitivity in patients receiving zinc-containing insulin products and copper hypersensitivity in women receiving copper-containing intrauterine devices, providing evidence that patients may experience hypersensitivity reactions when exposed to these metals. If hypersensitivity reactions (e.g., pruritis, angioedema, dyspnea, rash, urticaria) occur in patients receiving Multrys in parenteral nutrition, discontinue Multrys, and initiate appropriate medical treatment *[see Contraindications (4)]*.

6 ADVERSE REACTIONS

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

Adverse reactions with other components of parenteral nutrition solutions:

- Pulmonary embolism due to pulmonary vascular precipitates *[see Warnings and Precautions (5.1)]*
- Vein damage and thrombosis *[see Warnings and Precautions (5.2)]*
- Aluminum toxicity *[see Warnings and Precautions (5.5)]*

Adverse reactions with the use of trace elements administered parenterally or by other routes of administration:

- Neurologic toxicity with manganese *[see Warnings and Precautions (5.3)]*
- Hepatic accumulation of copper and manganese *[see Warnings and Precautions (5.4)]*
- Hypersensitivity reactions with zinc and copper *[see Warnings and Precautions (5.7)]*

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Multrys is approved for use in neonatal and pediatric patients weighing less than 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. Safety and dosing recommendations in pediatric patients less than 10 kg are based on published literature describing controlled studies of products containing zinc, copper, manganese, and selenium *[see Dosage and Administration (2.5)]*.

8.6 Hepatic Impairment

Copper is primarily excreted in the bile. Excretion is decreased in patients with cholestasis and/or cirrhosis. Manganese is presumed to be excreted in bile *[see Clinical Pharmacology (12.3)]*. Hepatic accumulation of copper and manganese has been reported with long-term administration of parenteral nutrition at dosages higher than recommended *[see Warnings and Precautions (5.4)]*.

For patients with cholestasis or cirrhosis, monitor hepatic and biliary function during long-term administration of Multrys.

If a patient develops signs or symptoms of hepatobiliary disease during use of Multrys, obtain serum concentrations of copper and ceruloplasmin as well as manganese whole blood concentrations; consider using individual trace element products in these patients.

10 OVERDOSAGE

There is no information on overdose-related toxicity with a fixed-combination trace element product. However, there are reports on overdosage in the literature for the individual trace elements. Management of overdosage is supportive care based on presenting signs and symptoms. Obtain blood samples for laboratory testing of the individual trace elements and ceruloplasmin for copper.

Zinc

Acute zinc toxicity was reported in an infant who received an inadvertent 1,000-fold overdose of zinc in parenteral nutrition that led to cardiac failure and death. Zinc toxicity in adult patients receiving 17 to 400-fold the recommended dosage in parenteral nutrition for 2.5 to 60 days reported signs and symptoms including vomiting, diarrhea, hyperamylasemia, thrombocytopenia, and anemia. The zinc serum concentration was 2 to 30-fold the upper end of the reported range in healthy subjects in these cases.

Copper

Acute copper toxicity was reported in patients with oral, intravenous, or subcutaneous administration. Clinical manifestations included metallic taste, nausea, vomiting, abdominal pain, and multi-organ failure involving kidney, liver, blood, and cardiovascular systems. Chelating agents can be used for treatment of acute toxicity. Long-term administration of parenteral copper above recommended dosage may result in significant accumulation of copper in the liver, brain, and other tissues with possible organ damage *[see Warnings and Precautions (5.4)]*.

Manganese

Acute manganese toxicity was reported in adult patients following infusion of manganese more than 10,000-fold the recommended dosage and after use of dialysis fluid contaminated with manganese. Signs and symptoms included skin flushing, acute pancreatitis, elevated whole blood manganese concentrations, and MRI evidence of brain accumulation of manganese. Chronic infusion and oral intake of manganese above recommended dosage have resulted in neuropsychiatric symptoms and MRI evidence of brain accumulation of manganese *[see Warnings and Precautions (5.3)]*.

Selenium

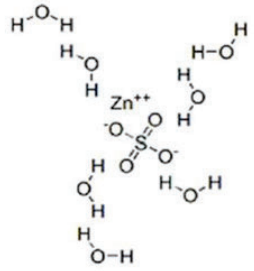
Acute selenium toxicity was reported with oral overdosage of greater than 1 g/day. Symptoms included nausea, vomiting, diarrhea, abdominal pain, garlic breath odor, and altered mental status. Death from circulatory collapse was reported after oral ingestion of 5 to 10 g of selenium with blood concentrations ranging 10 to 50-fold the upper end of the reported range in healthy subjects.

11 DESCRIPTION

Multrys (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.

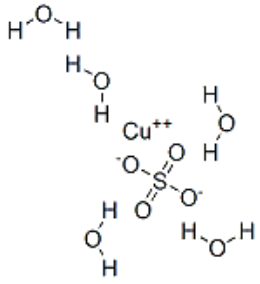
Each single-dose vial contains 1 mL. *Each mL contains zinc 1,000 mcg (equivalent to zinc sulfate 2,470 mcg), copper 60 mcg (equivalent to cupric sulfate 150 mcg), manganese 3 mcg (equivalent to manganese sulfate 8.22 mcg), selenium 6 mcg (equivalent to selenious acid 9.8 mcg), and water for injection. Sulfuric acid may be added to adjust pH between 1.5 and 3.5.

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



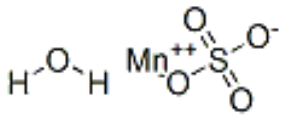
Molecular formula: $ZnSO_4 \cdot 7H_2O$.
Molecular weight: 287.54 g/mol.

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



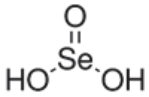
Molecular formula: $CuSO_4 \cdot 5H_2O$.
Molecular weight: 249.69 g/mol.

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.

Multrys contains no more than 1,500 mcg/L of aluminum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zinc

Zinc functions as a cofactor of various enzymes including DNA polymerases, RNA polymerases, alcohol dehydrogenase, and alkaline phosphatases. Zinc is a coordinator of protein structural folding that interacts with a variety of proteins, lipids, and nucleic acids. In addition, zinc is a catalyst of essential biochemical reactions, including activation of substrates of carbonic anhydrase in erythrocyte.

Copper

Copper is a cofactor for many metalloenzymes acting as an oxidase to achieve reduction of molecular oxygen. Examples of copper metalloenzymes include but are not limited to lysyl oxidase, monoamine oxidase, ferroxidase, cytochrome C oxidase, dopamine beta monooxygenase, tyrosinase, and superoxide dismutase.

Manganese

Manganese is essential for the normal catalytic activity of several metalloenzymes including manganese superoxide dismutase, arginase, glutamine synthetase, phosphoenolpyruvate decarboxylase, and pyruvate carboxylase. Manganese contributes to the normal function of several other enzyme families including the oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases.

Selenium

Selenious acid is converted in vivo to hydrogen selenide via glutathione-involved electron reductions. Hydrogen selenide acts as a selenium pool to form selenoproteins which include, but are not limited to, glutathione peroxidase, iodothyronine deiodinase, peroxidase, and thioredoxins.

12.2 Pharmacodynamics

The exposure-response relationship and the time course of pharmacodynamic response are unknown for zinc, copper, manganese, and selenium.

12.3 Pharmacokinetics

Zinc
Over 85% of total body zinc is found in skeletal muscle and bone. In blood, zinc is mainly localized within erythrocytes. Approximately 80% of serum zinc is bound to albumin and the remainder to α-2-macroglobulin and amino acids. In adults, zinc is primarily excreted via the gastrointestinal tract and eliminated in the feces. A smaller amount of zinc is excreted via the kidneys in the urine. Urinary zinc excretion rates in very low birth weight preterm infants are relatively high in the neonatal period, and they decline to a level on a body weight basis that is similar to that of normal adults by two months of age.

Copper
In plasma, about 7% of copper is bound to albumin and amino acids. In the liver, about 93% of copper is bound to ceruloplasmin and released to the serum. Copper is excreted in bile and into the gastrointestinal tract where it is not reabsorbed. Copper is also eliminated through the kidneys.

Manganese
Manganese is widely distributed in body tissues including liver and specific brain regions such as the basal ganglia. The concentrations of manganese are higher in erythrocytes compared to the plasma or serum concentrations. In human plasma, manganese is bound to albumin and β_1-globulin. Manganese is found in human bile suggesting biliary excretion.

Selenium
In humans, 85% of intravenous administered ^{75}Se-sodium selenite was protein-bound within 4 to 6 hours and 95% by 24 hours.

16 HOW SUPPLIED/STORAGE AND HANDLING

Multrys (trace elements injection 4*, USP) is a clear, colorless to slightly blue solution supplied in:

- 1 mL single-dose vial (NDC 0517-9302-01) and packaged in trays containing 25 vials per tray (NDC 0517-9302-25).

*Each mL of Multrys contains zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg.

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)]*.

17 PATIENT COUNSELING INFORMATION

Inform patients, caregivers, and home healthcare providers of the following risks of Multrys:

- Pulmonary embolism due to pulmonary vascular precipitates *[see Warnings and Precautions (5.1)]*
- Vein damage and thrombosis *[see Warnings and Precautions (5.2)]*
- Neurologic toxicity with manganese *[see Warnings and Precautions (5.3)]*
- Hepatic accumulation of copper and manganese *[see Warnings and Precautions (5.4)]*
- Aluminum toxicity *[see Warnings and Precautions (5.5)]*
- Hypersensitivity reactions with zinc and copper *[see Warnings and Precautions (5.7)]*

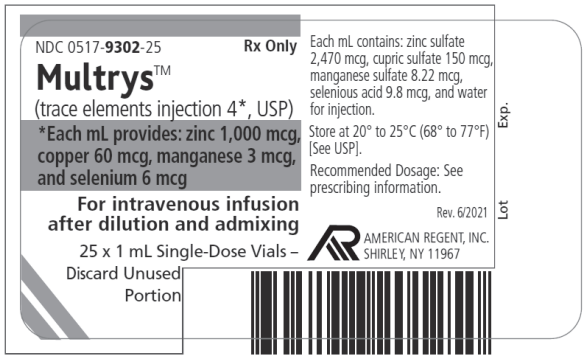
Manufactured by:

IN9302
Rev. 6/2021

NDA 209376
Multrys™ (Trace Elements Injection 4*, USP)
(zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg)
Applicant: American Regent, Inc.
Carton Labeling

Carton Labeling

Dimensions: 2.3125” W x 1.3125” H



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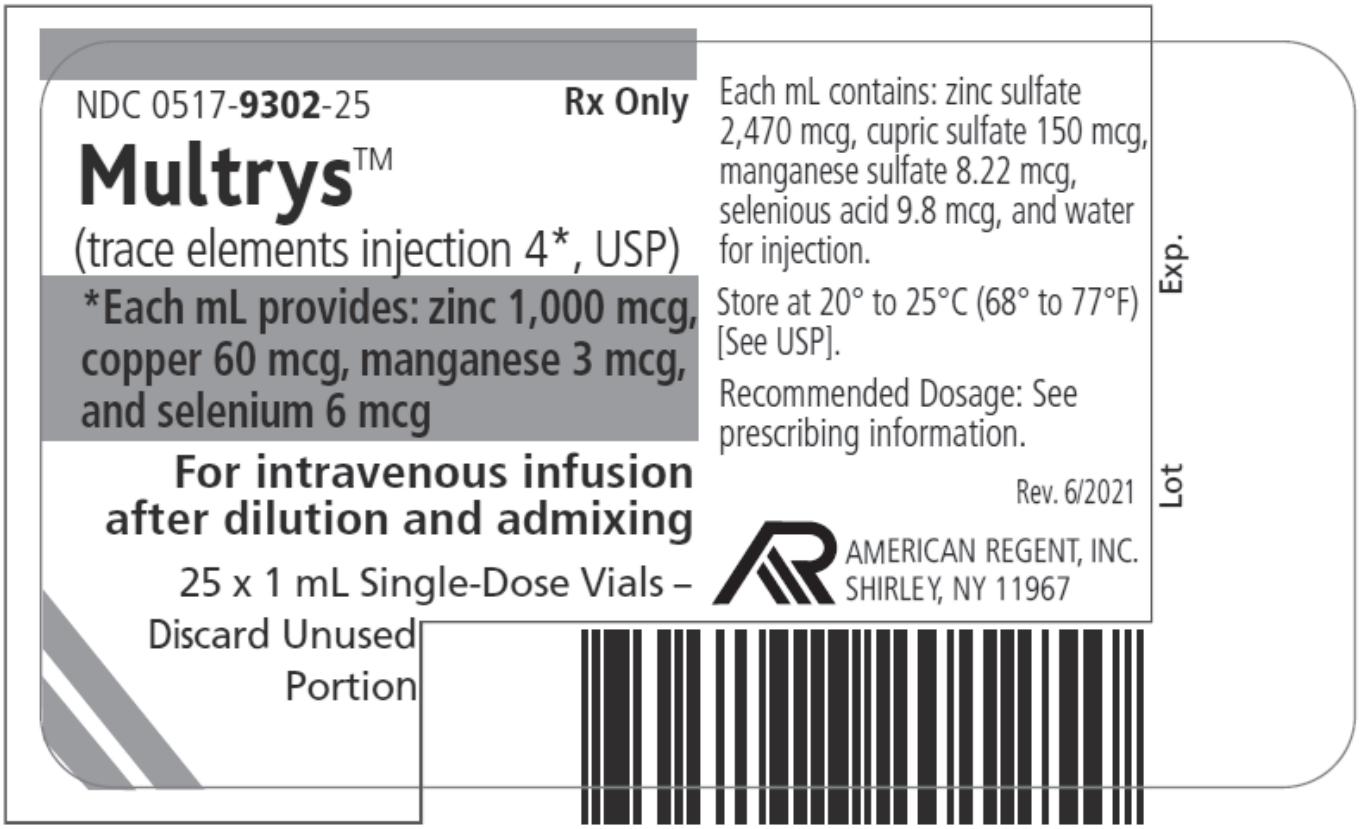
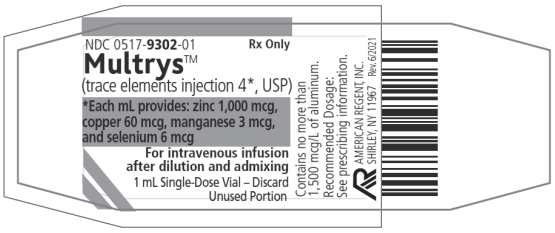


Note: The actual lot number and expiration date (MM-YYYY) will be imprinted on the far right side of the label during packaging.

NDA 209376
Multrys™ (Trace Elements Injection 4*, USP)
(zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg)
Applicant: American Regent, Inc.
Container Label

Container Label

Dimensions: 2” W x 0.7” H



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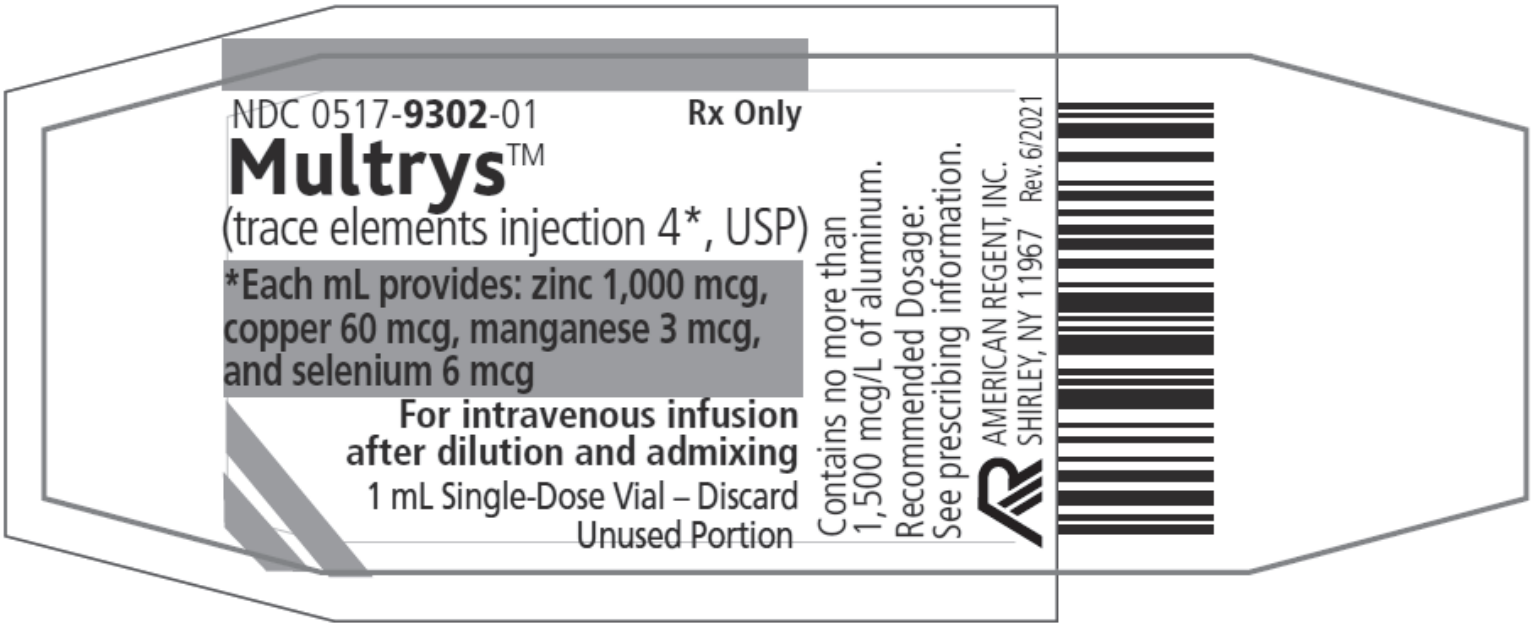

Note: The letters “LOT” and “EXP” along with the actual lot number and expiration date (MM-YYYY), will be imprinted to the far right side of the label during packaging.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209376Orig1s002

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	209376/S-002
Supporting document/s:	62, 87
Applicant's letter date:	12/11/2020; 05/21/2021
CDER stamp date:	12/11/2020; 05/21/2021
Product:	MULTRYS (trace elements injection 4*)
Indication:	For neonatal and pediatric patients weighing less than 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
Applicant:	American Regent, Inc.
Review Division:	Division of Hepatology and Nutrition (DHN)
Reviewer:	Ke Zhang, PhD
Supervisor/Team Leader:	David B. Joseph, PhD
Division Director:	Joseph G. Toerner, MD, MPH
Project Manager:	Thao Vu

1 Executive Summary

1.1 Introduction

Tralement (trace elements injection 4*) was approved in July 2020 for adult and pediatric patients weighing at least 10 kg as a source of zinc (Zn), copper (Cu), manganese (Mn), and selenium (Se) for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. Tralement contains 3000 µg Zn/mL, 300 µg Cu/mL, 55 µg Mn/mL, and 60 µg Se/mL. The current submission is a Prior Approval Supplement to support approval of an additional pediatric formulation, Multrys, for patients weighing less than 10 kilograms. Multrys contains 1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL. This Prior Approval Supplement was submitted to fulfill PMR 3877-02 that was required under PREA, as follows (approval letter dated 07/02/2020): *Develop a weight-appropriate formulation for pediatric patients weighing less than 10 kilograms.*

1.2 Brief Discussion of Nonclinical Findings

The original proposed acceptance criteria for each of the specified elemental impurities in the drug product (b) (4) provides a reasonable assurance of safety for the potential exposure from Multrys. In response to the Agency's Advice/ Information Request letter dated 06/25/2021, the Applicant agreed to reduce the acceptance criterion fo (b) (4) from not more than (NMT (b) (4) µg/mL to NMT (b) (4) µg/mL (amendment dated 06/25/2021). This change will reduce the risk of toxicit (b) (4) (b) (4) and is supported by the batch data (b) (4) (b) (4)

In addition, the Applicant's elemental impurities assessment included measurements of (b) (4) none of which were detected at or above their respective limits of quantification. The batch data for these potential elemental impurities provides a reasonable assurance of safety. No leachables assessment was conducted for Multrys. However, the leachables assessment conducted for Tralement, which is packaged in the same container-closure system, provides a reasonable assurance of safety for the potential exposure to organic leachables in the target patient population. The nonclinical review of the leachables assessment for Tralement is provided in the Multi-Disciplinary Review and Evaluation of NDA 209376, dated 07/02/2020.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical viewpoint, this supplement should be approved.

1.3.2 Additional Nonclinical Recommendations

This supplement fulfills PMR 3877-02.

1.3.3 Labeling

None

2 Drug Information

2.1 Drug

Multrys (trace elements injection 4*)

Zn 1000 mcg/mL, Cu 60 mcg/mL, Mn 3 mcg/mL, Se 6 mcg/mL

Pharmacologic Class: trace elements

2.2 Drug Formulation

Injection: 1 mL clear, colorless to slightly blue solution in a single-dose vial, which contains zinc 1 mg, copper 0.06 mg, manganese 3 mcg, and selenium 6 mcg.

2.3 Proposed Clinical Population and Dosing Regimen

Multrys is indicated in pediatric patients weighing less than 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. The Applicant's proposed dosing instructions are provided in the following tables (copied from the label). However, we anticipate that the final dosing instructions will be slightly different from what is shown in these tables, based on the current proposed revision of the label from the medical team. Regardless, the safety assessment of elemental impurities in Multrys can be based on the proposed dosing instructions below, since the calculated worst-case (maximum) exposure will be the same as the worst-case exposure resulting from the current revised dosing recommendations by the review team.

Table 1. (b) (4)

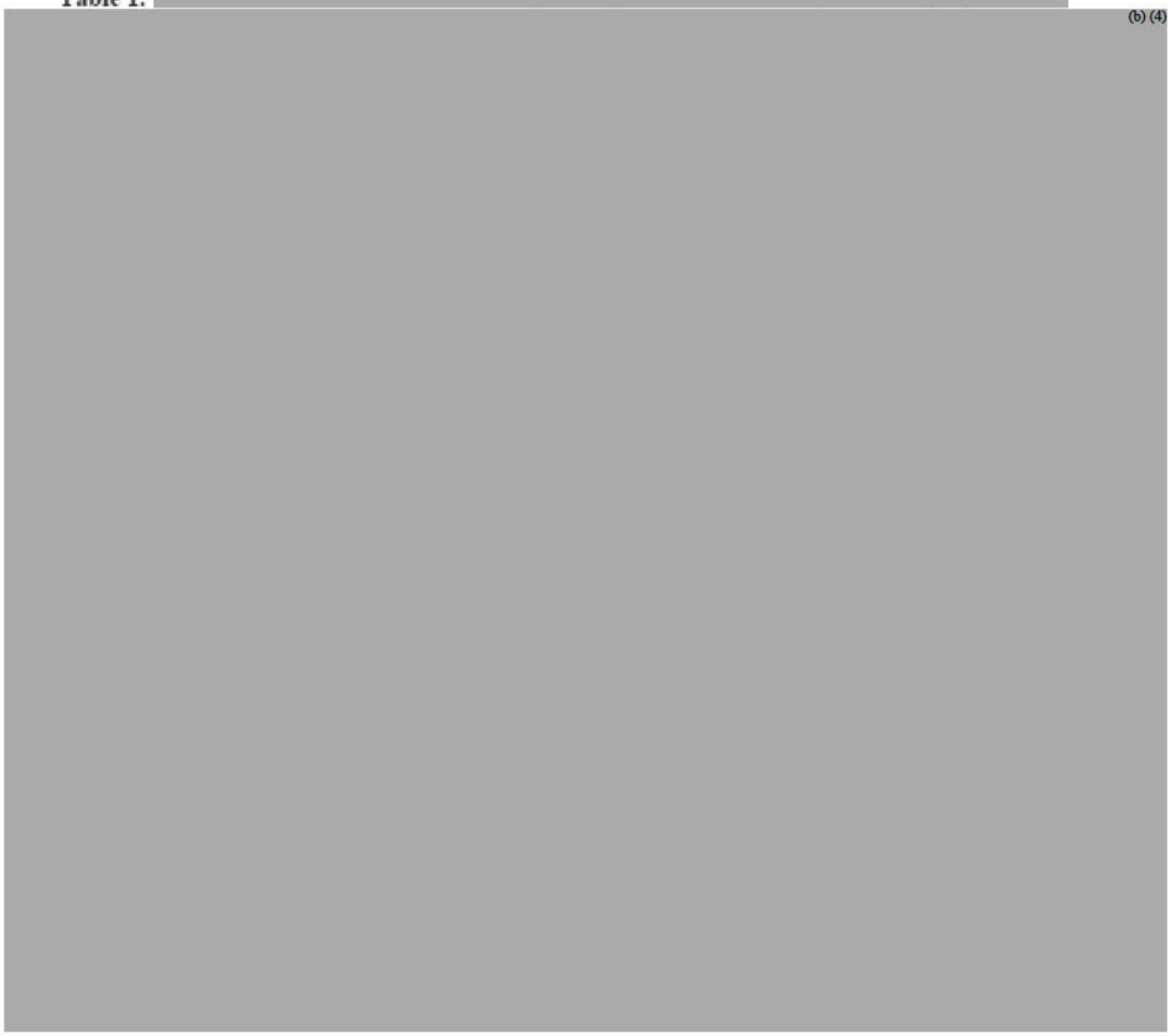

Table 2. (b) (4)

2.4 Regulatory Background

NDA 209376 for Tralement was approved for adult and pediatric patients weighing at least 10 kg, with a PREA PMR for development of a weight-appropriate formulation for pediatric patients weighing less than 10 kg. The current Prior Approval Supplement was submitted to fulfill the PMR (3877-02).

3 Studies Submitted

No nonclinical studies were submitted.

3.1 Studies Reviewed

Risk Assessment Summary for Potential Elemental Impurities in Trace Elements Injection 4*, USP (*1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL) (Study (b) (4) -PR-10-0017-S-1 submitted in the amendment dated 05/21/2021)

Drug Product Specifications

Since the active ingredients in the drug product are inorganic, the specifications do not contain acceptance criteria for drug-related compounds. Therefore, the nonclinical safety assessment of the drug product specifications is focused on the acceptance criteria for elemental impurities as shown in the Applicant's table below, which was provided in the original submission of this NDA supplement. It should be noted that the initially proposed tradename (b) (4) , is shown in the table heading, however the tradename "Mu e product.

Table 3.2.P.5.1-1 Finished Product Tests and Specifications for (b) (4) (1000 µg Zn/mL, 60 µg Cu/mL, 6 µg Se/mL, and 3 µg Mn/mL)

Test	Method	Specification
Aluminum	FP129	Not more than 1,500 µg/L
(b) (4)		
Elemental Impurities*	FP129 / (b) (4) 1559	<232> Meets requirements. (b) (4)
(b) (4)		
Volume in Container	FP129	<697> 1 mL fill: Not less than 1.0 mL
Bacterial Endotoxin	FP129	<85> The Endotoxin limit is not more than (b) (4) EU/mL
Sterility	FP129	<71> If no growth is observed, the article tested meets the requirements of the test for sterility.
Particulate Matter	FP129	<788> Meets the requirements (b) (4) (b) (4)
(b) (4)		The Elemental Impurity specifications may be revised in accordance with American Regent's Risk Assessment Summary.

The recommended dosage of Multrys by volume to be added to parenteral nutrition is based on body weight and ranges from (b) (4) mL/day up to a maximum of 1 mL/day. The resulting dose volume per kg in all weight band (b) (4) which will be used for the nonclinical safety assessment of elemental impurities that may be intentionally added in total parenteral nutrition (TPN) as nutritional supplement (b) (4) (b) (4)

Elemental Impurities

The Code of Federal Regulations provides labeling requirements for aluminum levels in large and small volume parenteral products used in TPN (21 CFR 201.323). The Applicant established the aluminum acceptance criterion at not more than 1500 mcg/L, which will limit the maximum daily dose of aluminum to 0.45 mcg/kg/day.

Previously, the Agency recommended that the amount of aluminum in this drug product be controlled to a limit not exceeding 0.6 mcg/kg/day (Written Response for Pre-IND 123432 dated December 13, 2017). Therefore, the proposed aluminum limit (1500 mcg/L) and the maximum potential aluminum dose of 0.45 mcg/kg/day are acceptable. The CMC reviewer for drug product (Dr. Le Zhang) confirmed that the Applicant's analytical method (ICP-MS) for aluminum was fully validated and is appropriate for its intended use.

Safety assessment of all other elemental impurities is divided into two categories: 1) elements not intentionally added in TPN as nutritional supplements; 2) elements that may be intentionally added in TPN as nutritional supplements. For elemental impurities in the first category, safety assessment of each element is based on compliance of the maximum daily dose with the Permitted Daily Exposure (PDE), as provided in International Conference on Harmonisation (ICH) Guidance Q3D(R1).

For safety assessment of elemental impurities, the Applicant analyzed three batches (# (b) (4) 20-005 (b) (4) 20-006, an (b) (4) 20-008) of Multrys drug produc (b) (4) (b) (4) (b) (4). The Applicant's table below provides the concentration limits needed to assure compliance with the PDE for all specified elemental impurities in the drug product, and the acceptance criteria in the specifications (listed under "American Regent Specification").

Table 3.2.P.5.6-2 Elemental Impurities Limits for (b) (4) (Trace Elements Injection 4*, USP) (1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL)

Element	Class	PDE Concentration Limit* (µg/mL)	American Regent Specification (µg/mL)
(b) (4)			

Table 3.2.P.5.6-2 Elemental Impurities Limits for (b) (4) (Trace Elements Injection 4*, USP) (1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL)

Element	Class	PDE Concentration Limit* (µg/mL)	American Regent Specification (µg/mL)
(b) (4)			

For elemental impurities which are not intentionally added in TPN as nutritional supplements, safety assessment is based on the maximum daily dose (1 mL) and the established PDE as provided in ICH Q3D(R1). The proposed limits for (b) (4) (b) (4) are acceptable (b) (4) (b) (4)

The drug product specifications also include acceptance criteria fo (b) (4)

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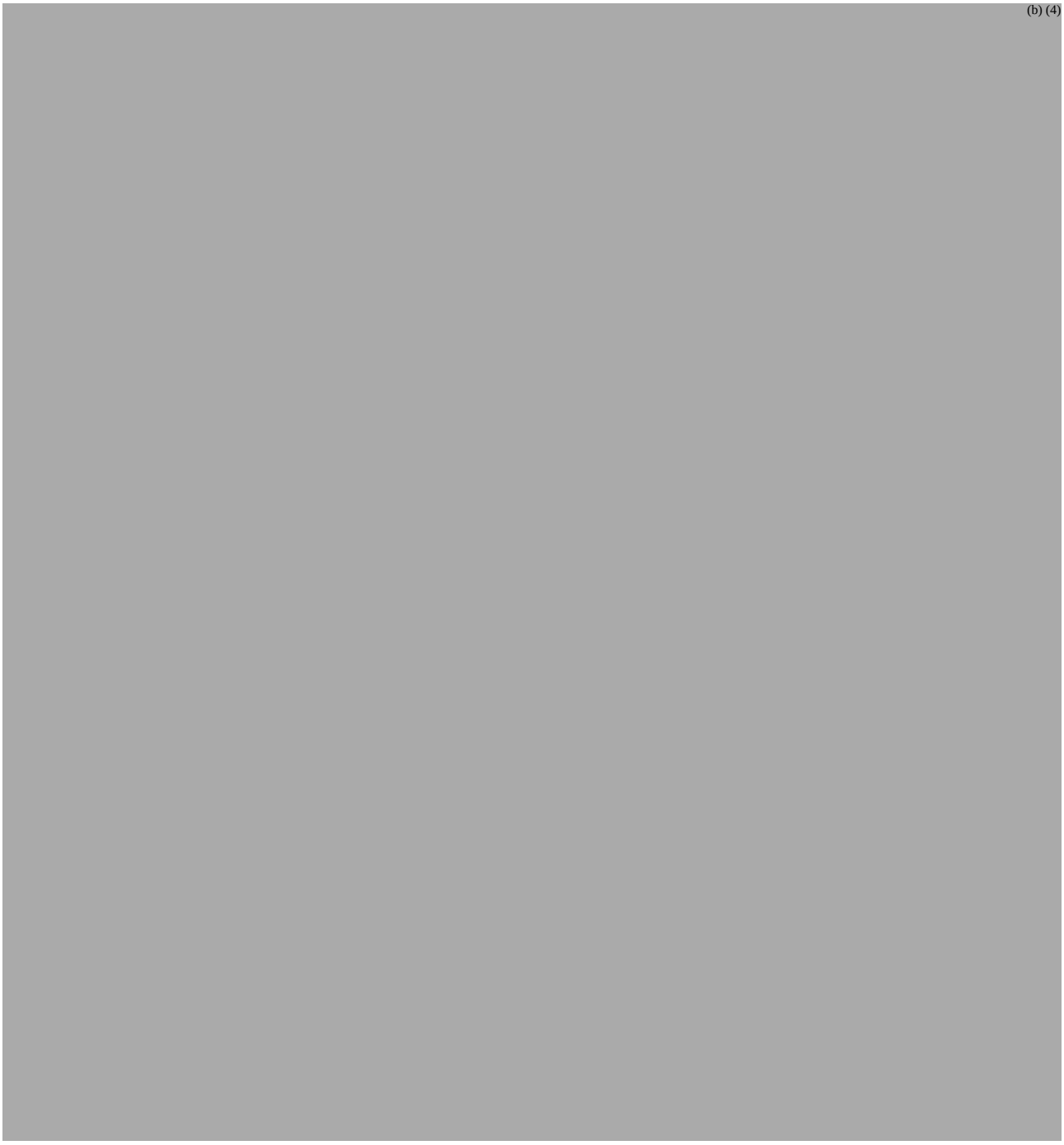

Leachables Assessment

Potential leachables/extractables from the glass vials an (b) (4) closures were assessed in the original NDA for the approved drug product (Tralement). The nonclinical team concluded there was no safety concern for organic leachables (NDA Multi-Disciplinary Review and Evaluation dated 07/02/2020, pp. 139-140). Multrys and Tralement are packaged in the same container closure system (vial and stopper). Because the maximum dose volume is 1 mL/day for both products, Multrys and

Tralement have the same analytical evaluation threshold (AET = 1.5 mcg/mL based on the Safety Concern Threshold of 1.5 mcg/day). Therefore, the Applicant is relying on leachables/extractables data from the approved drug product to support the approval of Multrys. The Applicant concluded that there is no safety concern for leachables based on 1 mL as the maximum total daily dose of Multrys. The Applicant's assessment is acceptable, and we agree that the leachables assessment for Tralement provides a reasonable assurance of safety for Multrys. The CMC reviewer for drug product (Dr. Le Zhang) agrees with the Applicant's reliance on the leachables data generated from studies with Tralement.

Summary of Nonclinical Product Quality Safety Assessment

Based on the Applicant's agreement to reduce th (b) (4) acceptance criterion from NMT (b) (4) µg/mL to NMT (b) (4) µg/mL, the revised drug product specifications provide a reasonable assurance of safety for the potential exposure to each of the specified elemental impurities in Multrys. Safety assessment for most of the specified elemental impurities was based on compliance of the worst-case exposures (mcg/day) with the respective PDE values. For example, the maximum potential exposures to (b) (4) (b) (4) (b) (4). The Applicant's elemental impurities assessment also included measurements o (b) (4) (b) (4), none of which were detected at or above their respective limits of quantification. Thus, the batch data for these potential elemental impurities provides a reasonable assurance of safety, as explained above. In addition, the proposed acceptance criterion for aluminum is acceptable, as explained above. Finally, there is a reasonable assurance of safety for the potential exposure to organic leachables, based on the justified extrapolation from the leachables data for Tralement.

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

/s/

KE ZHANG
06/28/2021 07:00:50 PM

DAVID B JOSEPH
06/28/2021 09:38:03 PM
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209376Orig1s002

OTHER REVIEW(S)

Division of Hepatology and Nutrition

REGULATORY PROJECT MANAGER and CLINICAL LABELING REVIEW

Applications:

Application	Supplement	Product Name	Date of Submission	Date of Receipt
NDA 209376	S-002	(b) (4) (trace elements injection 4*), Injection	12/11/2020	12/11/2020

Applicant: American Regent, Inc.

Labeling Reviewed:

Material	**Submit Date**	**Receipt Date**	**Compared to**
Prescribing Information (PI)	12/11/2020	12/11/2020	12/2020 last approved PI

Background and Summary Description

This Prior Approval supplemental new drug application provides for the addition of a new strength (1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL), and this new strength is to fulfill the following postmarketing requirement (PMR) under the Pediatric Research Equity Act (PREA) for:

PMR 3877-02: To develop a weight-appropriate formulation for pediatric patients weighing less than 10 kilograms.

Final report: 12/2020

Review

Regarding the new strength of 1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL developed under PREA PMR, PeRC concurred with the Division's assessment that the new strength fulfilled the above PREA PMR.

In the January 5, 2021 submission, the Applicant propose (b) (4) as the new proprietary name for this new strength. The Division and DMEPA raised safety concerns relating to the propose (b) (4) because this new strength (b) (4)

[redacted]. Therefore, we were concerned that the propose [redacted] may mislead healthcare providers [redacted]. The Division and DMEPA held a teleconference with the Applicant on Friday, March 12, 2021 to convey these concerns. The Applicant acknowledged the Agency's safety concerns and subsequently withdrew the proposed proprietary name [redacted] on March 16, 2021.On March 17, 2021 the Applicant proposed a new proprietary name "Multrys" for this new strength.

The existing approved strength of Tralement (zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg) is indicated for use in pediatric patients weighing at least 10 kg. The increased accuracy of dosing by volume using this new strength (1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL) in pediatric patients weighing < 10 kg would ultimately enhance the safety by "(1) allowing precise dosing and titration with automated equipment in admixing PN; (2) improving sterility by limiting the need for manual manipulation; and (3) minimizing dosing errors potentially introduced with manual manipulation", three main concerns raised during the review of the original NDA submission (refer to the Unireview of Tralement® dated 7/02/2020 in DARRTS). Thus, instructions regarding this new strength would be appropriate to include in the Dosage and Administration section of the labeling. DHN proposed adding the following language in Section 2.5 (underlined) to the PI, and the Applicant agreed. Please note that the rest of the PI language for this new strength "Multrys" are largely similar to the approved "Tralement" PI.

Rationale for recommended dosage in pediatric patients weighing < 0.59 kg

[redacted] Published literature provides evidence that excess Mn can accumulate in the central nervous system which can lead to brain injury and developmental delay. Therefore, the review teams proposed every other day dosing of Multrys of 0.2 mL (i.e., 200 µL) to be added to PN. This would achieve a safe dose of Mn in a volume that can be accurately added to the PN. However, every other day dosing of Multrys in this age group would result in a deficit of zinc, copper, and selenium that would likely lead to deficiencies of these trace elements Therefore, in the full prescribing information (FPI), the review team included Table 2 as noted below so that healthcare providers would know to supplement these trace elements while a neonate weighing < 0.6 kg is taking Multrys.

2.5 Recommended Dosage in Pediatric Patients and Monitoring Considerations

1 https://www.cdc.gov/growthcharts/clinical_charts.htm

Multrys is a fixed-combination product. Each mL of Multrys provides zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg.

Recommended Dosage for Pediatric Patients Weighing 0.4 kg to 0.59 kg

- The total recommended dosage of Multrys is 0.2 mL **every other day.**

- Daily supplementation of Zinc, Copper, and Selenium will be needed to meet daily requirements (See Table 2 below).

Recommended Dosage for Pediatric Patients Weighing 0.6 kg to less than 10 kg

- The recommended dosage of Multrys is 0.3 mL/kg/day rounded to nearest 0.1 mL for up to a maximum of 1 mL per day.

- The recommended volume of Multrys to be added to parenteral nutrition ranges from 0.2 mL per day to 1 mL per day based on body weight, see Table 1 below.

Table 1. Recommended Daily Volume of Multrys and Corresponding Amount of Each Trace Element (mcg)

Body Weight	Recommended Daily Volume	Amount of Trace Element Provided by the Corresponding Multrys Volume			
		Zinc mcg	Copper mcg	Manganese mcg	Selenium mcg
0.6 kg to 0.8 kg	**0.2 mL**	200	12	0.6	1.2
0.9 kg to 1.1 kg	**0.3 mL**	300	18	0.9	1.8
1.2 kg to 1.4 kg	**0.4 mL**	400	24	1.2	2.4
1.5 kg to 1.7 kg	**0.5 mL**	500	30	1.5	3
1.8 kg to 2 kg	**0.6 mL**	600	36	1.8	3.6
2.1 kg to 2.3 kg	**0.7 mL**	700	42	2.1	4.2
2.4 kg to 2.6 kg	**0.8 mL**	800	48	2.4	4.8
2.7 kg to 2.9 kg	**0.9 mL**	900	54	2.7	5.4
3 kg to 9.9 kg	**1 mL**	1,000	60	3	6

Additional Trace Element Supplementation with Multrys

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

- To determine the additional amount of supplementation that is needed, compare the calculated daily recommended dosage based on the body weight of the patient to the amount of each trace element provided by Multrys and enteral nutrition sources.

Table 2: Daily Requirement for Trace Element Supplementation for Pediatric Patients

Trace Element	Patient Weight (kg)	Daily Requirement*
Zinc	Less than 3 kg	400 mcg/kg/day
	3 kg to 5 kg	250 mcg/kg/day
	5 to 10 kg	100 mcg/kg/day
Copper	-	20 mcg/kg/day
Selenium	-	2 mcg/kg/day
Manganese**	-	1 mcg/kg/day

*Multrys is not recommended for pediatric patients who may require a lower dosage of one or more of these individual trace elements.
**Avoid additional manganese supplementation with Multrys use. Accumulation of manganese in the brain can occur with long-term administration with higher than the recommended dosage of 1 mcg/kg/day *[see Warnings and Precautions (5.3)].*

For pediatric patients weighing less than 3 kg, Multrys does not provide the recommended daily dosage of zinc.

- Zinc: For patients weighing less than 3 kg, add Zinc Sulfate to provide total daily recommended dose of 400 mcg/kg/day using parenteral and/or enteral routes of administration.

For pediatric patients weighing 0.4 kg to 0.59 kg and 4 kg to 9.9 kg, Multrys does not provide the recommended daily dosage of copper or selenium.

- Copper: For patients weighing 0.4 to 0.59 kg or 4 kg to 9.9 kg, add Cupric Chloride to provide total daily recommended dose of 20 mcg/kg/day using parenteral and/or enteral routes of administration.

- Selenium: For patients weighing 0.4 to 0.59 kg or 4 kg to 9.9 kg, add Selenious Acid to provide total daily recommended dose of 2 mcg/kg/day using parenteral and/or enteral routes of administration.

Monitoring

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

- Trace element 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.

Warnings and Precautions section 5.7

One other section of labeling that was substantially revised was Warnings and Precautions section 5.7 "Hypersensitivity Reactions with Zinc and Copper". The text was simplified, and extensive description of the symptoms of hypersensitivity were shortened because this clinical background information is not needed in labeling.

5.7 Hypersensitivity Reactions with Zinc and Copper

Postmarket safety reporting has identified zinc hypersensitivity in patients receiving zinc-containing insulin products and copper hypersensitivity in women receiving copper-containing intrauterine devices, providing evidence that patients may experience hypersensitivity reactions when exposed to these metals. If hypersensitivity reactions (e.g., pruritis, angioedema, dyspnea, rash, urticaria) occur in patients receiving Multrys in parenteral nutrition, discontinue Multrys, and initiate appropriate medical treatment *[see Contraindications (4)]*.

The labeling was sent to the Applicant on May 6, 2021 and May 19, 2021; and we received the agreed upon labeling on May 12, 2021 and May 19, 2021.

The DMEPA team reviewed the PI and Carton & Container Labels and provided recommendations in the labeling sent to the applicant on May 6, 2021 and May 13, 2021. The sponsor agreed with the recommendations and submitted the revised Carton & Container Labels which were reviewed by DMEPA (Dr. Sherly Abraham's review dated June 7, 20221 in DARRTS).

Prescribing Information

The version of the PI submitted on May 19, 2021 is considered to be final.

Recommendation(s)

This supplement is recommended for approval.

Reviewers

Thao Vu, R.Ph., Regulatory Project Manager, DHN
Ashish Dhawan, M.D., Medical Officer, DHN
Judith A. Racoosin, M.D., M.P.H., Deputy Director for Safety, DHN

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/s/

THAO M VU
06/29/2021 10:51:27 AM

ASHISH DHAWAN
06/29/2021 10:52:54 AM

JUDITH A RACOOSIN
06/29/2021 12:14:39 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	June 4, 2021
Requesting Office or Division:	Division of Hepatology and Nutrition (DHN)
Application Type and Number:	NDA 209376/S-002
Product Name and Strength:	Multrys (trace elements injection), zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg per mL[a]
Applicant/Sponsor Name:	American Regent, Inc.
OSE RCM #:	2020-2673-2
DMEPA Safety Evaluator:	Sherly Abraham, R. Ph.
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on June 2, 2021 for Multrys. Division of Hepatology and Nutrition (DHN) requested that we review the revised container label and carton labeling for Multrys (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The revised container label and carton labeling are acceptable from a medication error perspective. We have no further comments at this time.

[a]Proposed strength statement changed from (b) (4) (b) (4)' to 'each mL contains zinc 1000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg' during the review.

[b]Abraham, S. Label and Labeling Review for Multrys (NDA 209376/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 1. RCM No.: 2020-2673-1.

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/s/

SHERLY ABRAHAM
06/04/2021 04:24:06 PM

IDALIA E RYCHLIK
06/07/2021 10:25:14 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	June 1, 2021
Requesting Office or Division:	Division of Hepatology and Nutrition (DHN)
Application Type and Number:	NDA 209376/S-002
Product Name and Strength:	Multrys (trace elements injection), zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg per mL[a]
Applicant/Sponsor Name:	American Regent, Inc.
OSE RCM #:	2020-2673-1
DMEPA Safety Evaluator:	Sherly Abraham, R. Ph.
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on May 14, 2021 for Multrys. Division of Hepatology and Nutrition (DHN) requested that we review the revised container label and carton labeling for Multrys (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. Below, we have provided recommendations in Table 1 for the Applicant. We ask that the Division convey Table 1 in its entirety to American Regent, Inc so that recommendations are implemented prior to approval of this NDA Supplement.

[a] Proposed strength statement changed from (b) (4) to (b) (4) 'each mL contains zinc 1000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg' w.

[b] Abraham, S. Label and Labeling Review for Multrys (NDA 209376/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 1. RCM No.: 2020-2673

3 RECOMMENDATIONS FOR AMERICAN REGENT, INC.

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

Table 1. Identified Issues and Recommendations for American Regent, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The strength statement continues to lack prominence.	21 CFR 201.15(a)(6)	Increase the prominence of the strength statement. Box the product strength statement: "Each mL (b) (4)"
2.	As currently displayed, the net quantity statement is more prominent than the product strength statement.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is more prominent.	Decrease the prominence of net quantity statement; consider un-bolding the net quantity statement. Ensure that the net quantity statement does not compete for prominence with the product strength statement.
3.	Lack of clarity in package type and product handling instruction.	If the vial contains more drug than needed to provide the dose listed in the Dosage and Administration section of the PI, than the "Discard Unused Portion" statement should appear after the 'single-dose vial' statement to help mitigate drug use errors.	Consider re-aligning the "Single-Dose Vial" and "Discard Unused Portion" statements to read: "Single-Dose Vial – Discard Unused Portion" to minimize risk of the entire contents of the vial being given as a single dose.

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/s/

SHERLY ABRAHAM
06/01/2021 03:00:18 PM

IDALIA E RYCHLIK
06/01/2021 03:35:44 PM

LABEL AND LABELING REVIEW

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

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

Date of This Review:	April 1, 2021
Requesting Office or Division:	Division of Hepatology and Nutrition (DHN)
Application Type and Number:	NDA 209376/S-002
Product Name, Dosage Form, and Strength:	Multrys (trace elements injection 4*) *Each mL provides: zinc 1 mg, copper 0.06 mg, manganese 3 mcg, and selenium 6 mcg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	American Regent, Inc
FDA Received Date:	March 17, 2021 and March 18, 2021
OSE RCM #:	2020-2673
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

American Regent submitted a supplement for Multrys (trace elements injection 4*, USP [*contains: zinc, copper, manganese, and selenium]) to provide a new strength for neonatal and pediatric patients weighing less than 10 kg a source of zinc, copper, manganese, and selenium for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. Subsequently, DHN requested that we review the proposed Multrys prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 BACKGROUND OR REGULATORY HISTORY

American Regent submitted the proposed proprietary name (b) (4) for their supplement on January 5, 2021. According to American Regent (b) (4) (b) (4) the proposed product from the currently approved marketed product Tralement. On March 16, 2021, American Regent withdrew the proposed proprietary name (b) (4) and submitted a new proposed proprietary name, Multrys, on March 17, 2021.

3 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review

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

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Tables 2 and 3 below include the identified medication error issues with the submitted, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 1. Identified Issues and Recommendations for Multrys

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	Use of confusing symbols (i.e. ">" and "<")are noted throughout the PI.	These symbols may be mistaken as opposite of the intended meaning. The usage of symbols can cause misinterpretation and confusion.[a]	Replace the symbols with their intended meaning.
2.	A negative statement (b) (4) is identified in Dosage and Administration section in Highlights and Full Prescribing Information.	Due to our understanding of post-marketing reports, negative statements may have the opposite of intended meaning because the wor (b) (4) can be overlooked and the warning be misinterpreted as an affirmative action.[b] Additionally, this statement is inconsistent with the proposed carton labeling and container label.	Revise the negative statement (b) (4) to read 'Intravenous infusion after dilution and admixing only'.
3.	As currently stated, there is insufficient differentiation between the recommended dose frequency for patients weighin (b) (4) kg to (b) (4) kg	Lack of clarity. The recommended dosage for 0.4 kg to 0.59 kg is 0.2 mL *every other day* and the recommended dosage for	We recommend having a separate subsection in Highlights and Full Prescribing Information for 0.4 kg to 0.59 kg weigh range.

[a] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 Sep 16]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

[b] Institute for Safe medication practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Safe Alert Acute Care. 2010;15(16):1-3

Table 1. Identified Issues and Recommendations for Multrys			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	verses patients weighing [redacted] kg [redacted] mg. Dosing for patients who fall between [redacted] kg and [redacted] kg is omitted or unclear.	[redacted] kg t [redacted] kg is 0.2 mL [redacted]. The lack of prominence of the dose frequency difference may lead to potential medication administration errors and overdose or underdose.	For example, "Recommended Dosage for Neonatal/Pediatric Patients 0.4 kg to 0.59 kg" We further recommend to bold the frequency of administration "every other day".

Table 2. Identified Issues and Recommendations for American Regent, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label and Carton Labeling			
1.	The established name is not at least half the size of the proprietary name.	21 CFR 201.10(g)(2).	Revise the established name to be at least half the size of the proprietary name.
2.	The strength statement lacks prominence.	21 CFR 201.15(a)(6)	Increase the prominence of the strength statement.
3.	The net quantity statement is more prominent than the product strength statement and is located in close proximity to the product strength statement.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is more prominent and located in close proximity to the strength statement.	Decrease the prominence and relocate the net quantity statement away from the product strength, such as to the bottom corner of the principal display panel.
4.	The route of administration statement is misleading and may be improved to improve clarity.	We recommend this to minimize the risk of administering the drug as an intravenous bolus.	Consider revising the statemen [redacted]" to "For intravenous infusion after dilution and admixing".

Table 2. Identified Issues and Recommendations for American Regent, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
5.	The package type term, single-dose vial, is overtly prominent and the sentence "**discard unused portion**" is bolded.	Unnecessary prominence of package type term and discard statement takes the reader's attention away from other important information on the PDP such as the established name, dosage form statement and strength statement.	Revise the package type term by decreasing the font size and unbold the sentence, "discard unused portion".
Container Label			
1.	The usual dose statement is absent on the container label.	As per 21 CFR 201.55, the usual dose statement is required on the container label.	Add the usual dose statement, "Recommended Dosage: See prescribing information."
Carton Labeling			
1.	It is unclear where the machine-readable product identifier is located on the label. Additionally, the format of the human-readable portion of the product identifier is not identified.	The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.	The DSCSA guidance on product identifiers recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier. Include the machine-readable data matrix barcode and a human readable product identifier to the carton labeling. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following: **NDC: [insert NDC]** **SERIAL: [insert serial number]**

Table 2. Identified Issues and Recommendations for American Regent, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			LOT: [insert lot number] **EXP: [insert expiration date]** We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

5 CONCLUSION

Our evaluation of the proposed Multrys PI, container label, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 1 for the Division and Table for the Applicant. We ask that the Division convey Table in its entirety to American Regent, Inc so that recommendations are implemented prior to approval of this NDA Supplement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Multrys received on March 18, 2021, from American Regent, Inc.

Table 2: Relevant Product Information for Multrys	
Initial Approval Date	N/A
Active Ingredient	Zinc, copper, manganese, and selenium
Indication	Multrys is a combination of trace elements (zinc sulfate, cupric sulfate, manganese sulfate and selenious acid) indicated in neonatal and pediatric patients weighing less than 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.
Route of Administration	Intravenous
Dosage Form	injection
Strength	*Each mL provides: zinc 1 mg, copper 0.06 mg, manganese 3 mcg, and selenium 6 mcg
Dose and Frequency	Multrys is a fixed dose-combination product. For infants weighing 0.4 kg to 0.59 kg is 0.2 mL every other day. For pediatric patients weighing 0.6 kg to less than 10 kg, the recommended dosage of Multrys (b) (4) mL/kg/day, with a cap of 1 mL per day added to parenteral nutrition (zinc 1 mg/copper 0.06 mg/manganese 3 mcg/selenium 6 mcg).
How Supplied	1 mL single-dose vials (NDC 0517-9302-01). It is packaged in trays containing 25 vials per tray (NDC 0517-9302-25).
Storage	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)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 31, 2021 , we searched for previous DMEPA reviews relevant to this current review using the terms, Tralement. Our search identified four previous reviews[c,d,e,f] and we confirmed that our previous recommendations were implemented.

APPEARS THIS WAY ON ORIGINAL

[c] Vee S. Label and Labeling Review for Tralement (NDA 209376/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 21. RCM No.: 2020-1681.

[d] Vee S. Label and Labeling Review for Tralement (NDA 209376/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEP 9. RCM No.: 2020-1681-1

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

[f] Vee, S. Label and Labeling Review for Tralement (NDA 209376). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 30. RCM No.: 2019-1889-1.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

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

- Vial label received on March 17, 2021
- Tray labeling received on March 17, 2021
- Prescribing Information (Image not shown) received on March 18, 2021, available from \\CDSESUB1\evsprod\nda209376\0059\m1\us\114-labeling\draft\labeling\prescribing-info-in9302-rev-3-2021-tracked-changes-word.docx
-

G.2 Label and Labeling Images

Vial label

Enlarged

Tray Labeling

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

Enlarged

Note: The actual lot number and expiration date (MM-YYYY) will be imprinted to the far right side of the label during packaging.

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/s/

SHERLY ABRAHAM
04/01/2021 03:13:55 PM

IDALIA E RYCHLIK
04/01/2021 03:21:00 PM

Memorandum (Neonatal-Perinatal Medicine Consultation)

To: Ashish Dhawan MD MSPH; Medical Officer / Clinical Reviewer
Thao Vu, RPh; Regulatory Project Manager
DHN/OII/OND/CDER

From: An N. Massaro, MD
Medical Officer, Office of Pediatric Therapeutics, OCPP/OC

Through: Gerri R. Baer, MD
Supervisory Medical Officer, Office of Pediatric Therapeutics, OCPP/OC

Susan McCune, MD
Director, Office of Pediatric Therapeutics, OCPP/OC

Date: March 1, 2021

Subject: Neonatal-Perinatal Medicine Consultation – NDA 20937 (b) (4) S-002

MATERIALS REVIEWED:

1. NDA 209376/S-002 Prior Approval Supplement – Addition o (b) (4) (Trace Elements Injection 4*, USP) (1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL) Pediatric Formulation to the Approved NDA; Dated December 11, 2020
2. NDA Multi-disciplinary Review and Evaluation–NDA 209376 TRALEMENT (trace elements injection 4*), dated July 2, 2020
3. Neonatal-Perinatal Consultation on NDA 209376; Dr. Gerri Baer, dated April 24, 2020

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

NEONATAL-PERINATAL MEDICINE CONSULTATION QUESTION(S):

From Consult Request:

NDA 209376 (Tralement) was approved on 7/2/2020 indicated in adult and pediatric patients weighing at least 10 kg, as a source of zinc, copper, manganese, and selenium. Formulation approved in the NDA was 3 mg Zn/mL, 0.3 mg Cu/mL, 55 µg Mn/mL, and 60 µg Se/mL. With this approval, the DHN issued a PREA PMR 3877-02: to develop a weight-appropriate formulation for pediatric patients weighing less than 10 kilograms. The Applicant submitted S-002 on 12/11/2020 proposed to add a new formulation, (1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL) and to fulfill the PREA PMR requirements.

DHN requests OPT's assistance to review and determine the appropriate dosing to support the neonatal population.

BACKGROUND:

Product Description and Regulatory History

After recommendations from the American Society of Parenteral and Enteral Nutrition (ASPEN) to reformulate parenteral multivitamin and trace element products dating back to 2012-2013 (b) (4) (b) (4) Commonly used parenteral nutrition (PN) additives "Multitrace-4 Neonatal" and Multitrace-4 Pediatric" are marketed unapproved products.

Tralement™ (NDA209376) is a combination of trace elements (zinc sulfate, cupric sulfate, manganese sulfate and selenious acid) for parenteral nutrition which was approved in July 2020. An OPT Neonatal-Perinatal Medicine consultation provided in April 2020 included overview of neonatal dosing considerations for each trace element in Tralement, including referenced weight-based dosing recommendations for preterm and term neonates and toxicities related to excessive dosing. Given that the approved formulation did not provide appropriate dosing for pediatric patients weighing less than 10 kg, development of a neonatal formulation was planned, and PREA PMR 3877-02 was issued (b) (4) (S-002) is submitted as a new formulation (1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL) to fulfill this PMR.

Multi-disciplinary Review and Evaluation for NDA 209376 included extensive discussion of dosing for the individual trace element components of Tralement including consideration of FDA labeling for Zinc Sulfate (NDA 209377, approved July 18, 2019), Cupric Chloride (NDA 018960, approved June 26, 1986), and Selenious Acid (NDA 209379, approved April 30, 2019), as well as extensive literature review including consensus recommendations from various specialty organizations including the Institute of Medicine, ASPEN,[1,2] and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).[3] The summary table below, adapted from the NDA 209376 Integrated Review, is included for reference.

Table 1. Neonatal Trace Element Dosing Recommendations

Element	Zn	Cu	Mn	Se
Dose Range for Preterm or LBW Neonates	FDA Labeling <3 kg 400 mcg/kg/d ASPEN 400 mcg/kg/d ESPGHAN 400-500 mcg/kg/d	FDA Labeling 20 mcg/kg/d ASPEN 20 mcg/kg/d ESPGHAN 20 mcg/kg/d	FDA Labeling N/A ASPEN 1 mcg/kg/d ESPGHAN ≤1 mcg/kg/d	FDA Labeling <7 kg 2-4 mcg/kg/d ASPEN 2 mcg/kg/d ESPGHAN 7 mcg/kg/d
Dose Range for Term Neonates-Infants	FDA Labeling 3-5 kg 250 mcg/kg 5-10 kg 100 mcg/kg ASPEN 3-10 kg 250 mcg/kg/d ESPGHAN <3 mo 250 mcg/kg/g >3 mo 100 mcg/kg/d	FDA Labeling 20 mcg/kg/d ASPEN 20 mcg/kg/d ESPGHAN 20 mcg/kg/d	FDA Labeling N/A ASPEN 1 mcg/kg/d ESPGHAN ≤1 mcg/kg/d	FDA Labeling <7 kg 2-4 mcg/kg/d ≥7 kg 2 mcg/kg/d ASPEN 2 mcg/kg/d ESPGHAN 2-3 mcg/kg/d

Proposed Indication for Use

(b) (4) is indicated in pediatric patients weighing less than 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.

Proposed Dosing *(from Sponsor draft labeling)*

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- (b) (4)
-

Reviewer Comments: *The Sponsor's proposed dosing table has calculation and formatting errors (highlighted in red above) and the accompanying instructions for additional supplementation are not presented clearly for prescribers. The rationale for the weight bands chosen in the dosing table is unclear as the selected cutoffs do not optimize dosing for Zinc, Copper and Selenium while limiting Manganese to ≤1mcg/kg/day. Alternate weight bands are suggested below that provide more consistent target dosing for each dose volume. Suggested changes are highlighted in yellow.*

(b) (4)

We agree that instructions should include additional supplementation of Zinc for infants <3kg and Copper and Selenium for infants in the higher weight bands, as the recommended dosing o (b) (4) *does not meet daily requirements. We also agree that there is no need to provide additional Manganese even though the higher weight bands will receive <1mcg/kg, given the known risk for neurotoxicity related to manganese accumulation.*[2,4] *However, the instructions provided in the proposed labeling are unclear. Rather than* (b) (4) (b) (4) *we recommend that providers be instructed to provide additional single ingredient supplementation to meet recommended daily dosage* (b) (4)

(b) (4)

(b) (4)

While data are not definitive regarding the threshold for dose and duration of exposure that can lead to significant Manganese accumulation and CNS deposition, or the reversibility of this complication,[2,4] we believe that the maximum dose of 1mcg/kg/day should be observed particularly in the extremely low birth weight preterm infant in whom hepatic immaturity may further contribute to vulnerability to manganese toxicity. Thus, the current formulation provides appropriate dosing down to 0.6 kg only. While a dose o (b) (4) *mL may be more appropriate with regards to manganese dosing for the* (b) (4) *it is unclear whether this can be reliably measured by standard equipment in most TPN formulating pharmacies* (b) (4)

(b) (4)

(b) (4)

It may also be considered whether dosing t (b) (4) *o* (b) (4) *could be used in the higher weight bands. This would allow for more infants to be appropriately dosed with the combination product without the need to supplement individual ingredients, as supplementing additional ingredients may lead to*

medication erro (b) (4)

(b) (4)

(b) (4)

Safety of excipients and potential contaminant (b) (4) dose would need to be confirmed. If this is acceptable, then labeling would need to specify additional copper and selenium supplementation fo (b) (4) to 9.9 kg only. Additionally, labeling would need to specify more frequent zinc level monitoring fo (b) (4) kg to monitor for elevated levels.

ANALYSIS/RESPONSE:

As formulate (b) (4) provides appropriate weight-based dosing of zinc fo (b) (4) kg, of copper and selenium fo (b) (4) kg and of manganese fo (b) (4) kg. Proposed dosing fo (b) (4) will provide more than the maximum recommended dose of Manganese. Additional

supplementation of individual trace elements will be required for certain weight bands with the proposed formulation. Specifically, zinc supplementation will be needed for infants <3 kg and copper and selenium supplementation will be needed fo (b) (4) kg. Alternatively (b) (4) then copper and selenium supplementation will only be needed fo (b) (4) kg. While this approach may provide higher doses of zinc for patient (b) (4) to (b) (4) kg (which may be mitigated by zinc level monitoring), this may allow for adequate dosing wit (b) (4) across a wider range of patient (b) (4) (b) (4) It should also be noted that this product is intended fo (b) (4) . Therefore, the proposed proprietary nam (b) (4) should be reconsidered (b) (4) (b) (4)

RECOMMENDATIONS:

1. Corrections and adjustments to the weight-based dosing administration table fo (b) (4) (b) (4)
2. Instructions for recommended supplementation should be simplified. We recommend listing the weight ranges that require supplementation and the total recommended daily dose for providers to calculate specific dosing needed to meet requirements.
3. *Dosing of Manganes* (b) (4) *should not exceed 1 mcg/kg/day* (b) (4) (b) (4) (b) (4) Alternatively, dosing the current formulation a (b) (4) 0.2mL every other day can be considered although this would require additional supplementation of Zinc, Copper and Selenium to meet requirement (b) (4)
4. (b) (4) maximum dose should be considered, *if safety of excipients and contaminants can be confirmed,* in order to provide dosing o (b) (4) across a wider range of patients without need for additional supplementatio (b) (4) (b) (4)
5. We recommend revising the product name (b) (4) (b) (4) We sugges (b) (4) or (b) (4)

REFERENCES:

1. Vanek VW, Borum P, Buchman A, et al. A.S.P.E.N. position paper: recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. *Nutr Clin Pract.* 2012;27(4):440-491.
2. Vanek VW, Borum P, Buchman A, et al. A Call to Action to Bring Safer Parenteral Micronutrient Products to the U.S. Market. *Nutr Clin Pract.* 2015;30(4):559-569.
3. Domellof M, Szitanyi P, Simchowitz V, Franz A, Mimouni F, nutrition EEECwgopp. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Iron and trace minerals. *Clin Nutr.* 2018;37(6 Pt B):2354-2359.
4. Zemrani B, McCallum Z, Bines JE. Trace Element Provision in Parenteral Nutrition in Children: One Size Does Not Fit All. *Nutrients.* 2018;10(11).
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/s/

AN N MASSARO
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209376Orig1s002

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	May 12, 2021
Application Type and Number:	NDA 209376/S-002
Product Name and Strength[a]:	Multrys (trace elements injection) injection, zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg per mL[a]
Product Type:	Multiple Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	American Regent, Inc (American Regent)
Panorama/PNR ID #:	2021-1044723877
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.
Associate Director of Nomenclature and Labeling:	Mishale Mistry, Pharm.D., MPH

[a]Proposed strength statement changed from (b) (4) (b) (4) 'each mL contains zinc 1000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg' during the review.

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Multrys, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary name are outlined in the reference section and Appendix A respectively. American Regent submitted an external name study, conducted b [redacted] for this proposed proprietary name.

1.1 REGULATORY HISTORY

American Regent submitted a supplement on January 5, 2021, proposing a new formulation intended for neonatal and pediatric patients weighing less than 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. As part of the supplement, American Regent proposed the proprietary name [redacted] for the new formulation. According to American Regen [redacted] the proposed product from the currently marketed product, Tralement. On March 12, 2021, we held a teleconference with the Sponsor to notify American Regent of our preliminary safety concerns with their proposed [redacted]

On March 16, 2021, American Regent withdrew the proposed proprietary name [redacted] and submitted a new proposed proprietary name, Multrys, on March 17, 2021.

1.2 PRODUCT INFORMATION

The following product information for Multrys is provided in the proprietary name submission received on March 17, 2021 and prescribing information received on March 18, 2021.

Table 1. Product Information for Multrys and Tralement

Product Name	**Multrys**	**Tralement**[c]
Pronunciation	Mul trys	Tra-le-ment
Initial Approval Date	N/A	July 2, 2020
Active Ingredient	Zinc, copper, manganese, and selenium	

[b] Jackson, S. Tcon Meeting Minutes fo [redacted] NDA 209376/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 12. PNR ID: 2021-1044723877

[c] Tralement. Dailymed. Accessed on May 11, 2021: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a49ffb90-f307-433e-a86e-aaea6d6a9982

Indication	Multrys is indicated in neonatal and pediatric patients weighing less than 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.	Tralement is 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.
Route of Administration	Intravenous	
Dosage Form	injection	
Strength	Each mL contains zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg	Each mL provides zinc 3 mg, copper 0.3 mg, manganese 55 mcg, and selenium 60 mcg
Dose and Frequency	For infants weighing 0.4 kg to 0.59 kg: 0.2 mL every other day. For pediatric patients weighing 0.6 kg to less than 10 kg (b) (4) mL/kg/day, with a cap of 1 mL per day added to parenteral nutrition	Adults and Pediatric Patients weighing at least 50 kg: 1 mL per day added to parenteral nutrition. Tralement is not recommended for those patients who may require a lower dosage of one or more of the individual trace elements. Pediatric Patients Weighing 10 kg to 49 kg: based on body weight and ranges from 0.2 mL to 0.8 mL per day.
How Supplied	1 mL single-dose vials (NDC 0517-9302-01). It is packaged in trays containing 25 vials per tray (NDC 0517-9302-25).	
Storage	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)	

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name, Multrys.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Multrys would not misbrand the proposed product. OPDP noted the phonetic similarities of Multrys to the marketed unapproved product, Multitrace, and they deferred the safety decision to DMEPA. We evaluate the name pair below and in Appendix E. The Division of Hepatology and Nutrition (DHN) concurred with the findings of OPDP's assessment for Multrys.

Multrys vs. Multitrace-4 Neonatal/Multitrace-4 Pediatric/Multitrace-5:

Orthographically, the lengths of [root] names differ by three letters. Phonetically, the root name Multitrace has an additional syllable as compared to Multrys. The endings of the second syllables ('trys' vs.'ti') provide some phonetic differences. We note that Multitrace products have a modifier ('4 Neonatal', '4 Pediatric' or '5') that is absent in Multrys. Therefore, as Multitrace is not available under the root name alone, a modifier or product strength would need to be specified on a prescription/medication order. In addition to the orthographic and phonetic differences, we note that both Multrys and Multitrace products are considered high-alert medications which require safeguards at various points of the medication use process to reduce the risk of error. In clinical practice, additives for TPN solutions are typically ordered by the established names[d] using a TPN prescription/order program and it is not anticipated that Multrys and Multitrace products will be written on a medication order alone.

Therefore, in this instance, when all of the abovementioned factors are considered in totality, we find the risk of confusion is adequately minimized in this case.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Multrys.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proposed proprietary name[e].

2.2.2 Components of the Proposed Proprietary Name

American Regent indicated in their submission that the proposed proprietary name, Multrys, is a blend of multiple trace elements and close to the marketed unapproved Multitrace. This proprietary name is comprised of a single word. We note that Multrys includes the letter string '-tr-,' a medical abbreviation for "time-release". Although we typically discourage the inclusion of medical abbreviations in proprietary names, we determined that the location of the abbreviation, '-tr-,' in the beginning of suffix of the name is unlikely to be separated from the surrounding letters in a manner that would lead to confusion in this case. Thus, in this case, we do not object to the inclusion of the letter strings '-tr-' in the suffix of the proposed proprietary name.

2.2.3 Comments from Other Review Disciplines at Initial Review

On April 7, 2021, the Division of Hepatology and Nutrition (DHN) did not forward any comments or concerns relating to Multrys at the initial phase of the review.

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[d] **Multrys**: contains zinc, copper, manganese, and selenium; **Multitrace-4 Neonatal**: contains zinc, copper, manganese, and chromium; **Multitrace-4 Pediatric**: contains zinc, copper, manganese, and chromium; **Multitrace-5**: contains zinc, copper, manganese, chromium, and selenium

[e] USAN stem search conducted on April 5, 2021.

2.2.4 FDA Name Simulation Studies

Eighty-one (n=81) practitioners participated in DMEPA's prescription studies for Multrys. Appendix B contains the results from the prescription simulation studies. Two voice study participants interpreted the proposed proprietary name Multrys as 'Motris' and 'Moltris', which are close variations to the currently marketed product Motrin.

Orthographically, the suffixes ('trys' vs. 'rin') provide sufficient orthographic differences. Phonetically, the endings of the second syllables ('trys' vs.'rin') provide some differences. In addition to the orthographic and phonetic differences, the following product characteristics would help to minimize the risk of error:

- Multrys is a single strength product whereas Motrin is available in different strengths and dosage forms (tablets: 400 mg, 600 mg and 800 mg; oral suspension: 100 mg/5 mL). Therefore, a strength of Motrin would need to be specified on a prescription/ medication order, and the strengths do not overlap with the strength of Multrys.
- Multrys is available as an injection administered intravenously whereas Motrin is available as a tablet and oral suspension administered orally. Furthermore, there are various over-the-counter products under the family name of 'Motrin' (e.g., Motrin IB, Motrin Migraine, Motrin PM etc.). Therefore, the dosage form for Motrin would need to be specified and there is no overlap in dosage form or route of administration (if included on a prescription/ medication order), which further differentiates this family of products from the proposed product.
- Multrys will be used as an additive in TPN solutions, which in clinical practice, is considered a high-alert medication requiring special safeguards in various points of the medication use process to reduce the risk of error. Also, in clinical practice, additives for TPN solutions are typically ordered by the established name using a TPN prescription/ order program and it is not anticipated that Multrys will be written on a medication order alone. Additionally, there are compatibility considerations with TPN solutions.

Therefore, in this instance, when all of the abovementioned factors are considered in totality, we find the risk of confusion is adequately minimized in this case. We evaluate this name pair in Appendix E.

2.2.5 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Our POCA search[f] identified 58 names with a combined phonetic and orthographic score of ≥55% or an individual phonetic or orthographic score ≥70%. These names are included in Table 1 below.

[f] POCA search conducted on April 5, 2021 in version 4.4

2.2.6 *Names Retrieved for Review Organized by Name Pair Similarity*

Table 1 lists the number of names retrieved from our POCA search, FDA prescription simulation study, and Drug Safety Institute (DSI) external study. These name pairs are organized as highly similar, moderately similar or low similarity for further evaluation.

Table 1. Names Retrieved for Review Organized by Name Pair Similarity

Similarity Category	Number of Names
Highly similar name pair: combined match percentage score ≥70%	3
Moderately similar name pair: combined match percentage score ≥55% to ≤ 69%	58
Low similarity name pair: combined match percentage score ≤54%	1

2.2.7. *Discussion of Dual Proprietary Names*

American Regent intends to market the combination of trace elements (zinc sulfate, cupric sulfate, manganese sulfate and selenious acid) injection (NDA 209376/S-002) under the proposed dual proprietary name, Multrys for neonatal and pediatric patients weighing *less than 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. American Regent currently markets the combination of trace elements (zinc sulfate, cupric sulfate, manganese sulfate and selenious acid) injection (NDA 209376) under the approved proprietary name, Tralement, for 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. See Section 1.2 Product Information, Table 1 for a comparison of product characteristics between the proposed formulation Multrys, and the currently marketed formulation, Tralement.

We have evaluated the risks associated with the naming strategy of using a dual proprietary name and note that postmarketing experience with other drug products has shown concomitant therapy to be a common type of error when an active ingredient is marketed under two or more names. We note that an alternative to this proposed naming strategy is to (b) (4) (b) (4) However, post marketing experience show (b) (4) resulting in wrong drug medication error (b) (4) (b) (4) (b) (4)

(b) (4)

Multrys contain the same active ingredients in different concentrations, are single-strength products, are dosed based on weight, and the recommended dosing between the two formulations may overlap which can further contribute to the risk of wrong drug errors, excessive dosing in the infant, and adverse clinical outcomes.

Given these products will have different indications (patient populations), doses, and strengths, managing them under separate names may decrease the likelihood of confusion. Therefore, we do not object to the use of a dual proprietary name in this case. Any residual risk may be managed through label and labeling mitigations.

2.2.7 Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities

Our analysis of the 62 names contained in Table 1 determined none of the names will pose a risk for confusion with Multrys as described in Appendices C through H.

2.2.8 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Hepatology and Nutrition (DHN). At that time we also requested additional information or concerns that could inform our review. On May 7, 2021, the Division of Hepatology and Nutrition (DHN) stated no additional concerns with the proposed proprietary name, Multrys.

3 CONCLUSION

The proposed proprietary name, Multrys, is acceptable.

If you have any questions or need clarifications, please contact Shawnetta Jackson, OSE project manager, at 301-796-4952.

3.1 COMMENTS TO AMERICAN REGENT, INC

We have completed our review of the proposed proprietary name, Multrys, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your submission, received on March 17, 2021, are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. ***USAN Stems (https://www.ama-assn.org/about/united-states-adopted-names-approved-stems)***

   USAN Stems List contains all the recognized USAN stems.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. 6F[h]

[h] National Coordinating Council for Medication Error Reporting and Prevention. https://www.nccmerp.org/about-medication-errors Last accessed 10/05/2020.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	**Is this proprietary name used for another product that does not share at least one common active ingredient?**
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 55% threshold in POCA.

DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥55% to ≤ 69%.
- Low similarity: combined match percentage score ≤54%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
    - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names7F[i]. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.
    - Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form) may be limited when the strength or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).

[i] Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

   Four separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions, verbal pronunciation of the drug name or during computerized provider order entry. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify vulnerability of the proposed name to be misinterpreted by healthcare practitioners during written, verbal, or electronic prescribing.

   In order to evaluate the potential for misinterpretation of the proposed proprietary name during written, verbal, or electronic prescribing of the name, written inpatient medication orders, written outpatient prescriptions, verbal orders, and electronic orders are simulated, each consisting of a combination of marketed and unapproved drug products, including the proposed name.

d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

   The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

   Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.			
Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	**Y/N**	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	**Y/N**	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	**Y/N**	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	**Y/N**	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		

Y/N	Do the suffixes of the names appear dissimilar when scripted?		

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Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is ≥55% to ≤69%).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names **with** overlapping or similar strengths or doses.

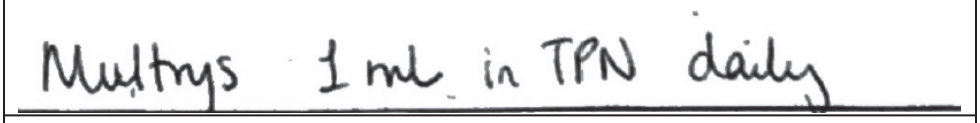
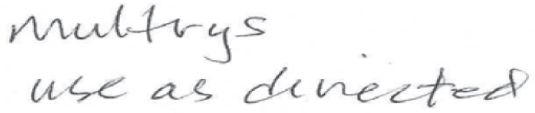
	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is ≤54%).

Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix B: **Prescription Simulation Samples and Results**

Figure 1. Multrys Study (Conducted on March 19, 2021)

Handwritten Medication Order/Prescription	**Verbal Prescription**
Medication Order:  	Multrys Use as directed
Outpatient Prescription:  	
CPOE Study Sample (displayed as sans-serif, 12-point, bold font)	
Multrys	

FDA Prescription Simulation Responses (Aggregate Report)

209 People Received Study

81 People Responded

Study Name: Multrys

Total	**21**	**18**	**26**	**16**	
INTERPRETATION	**OUTPATIENT**	**CPOE**	**VOICE**	**INPATIENT**	**TOTAL**
MOLTRES	0	0	2	0	2
MOLTRESS	0	0	7	0	7
MOLTRIS	0	0	1	0	1
MORTREX	0	0	1	0	1
MOTRIS	0	0	1	0	1
MUBTRYS	3	0	0	0	3

MULTRESS	0	0	5	0	5
MULTRIS	0	0	2	0	2
MULTRISS	0	0	1	0	1
MULTRYS	18	18	0	16	52
VOLTRES	0	0	1	0	1
VULTRES	0	0	1	0	1
VULTRESS	0	0	1	0	1
WOLTRIS	0	0	2	0	2
WOLTRISS	0	0	1	0	1

Appendix C: Highly Similar Names (e.g., combined POCA score is ≥70%)

No.	**Proposed name:** Multrys **Established name:** trace elements injection **Dosage form:** injection **Strength:** Each mL contains zinc 1000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg **Usual Dose:** 0.4 kg to 0.59 kg: 0.2 mL every other day. 0.6 kg to less than 10 kg: (b) (4) mL/kg/day, with a cap of 1 mL per day	**POCA Score (%)**	**Orthographic and/or phonetic differences in the names sufficient to prevent confusion** **Other prevention of failure mode expected to minimize the risk of confusion between these two names.**
1.	Multrys	100	The proposed name is the subject of the review.
2.	Ultrase	72	Name identified in RxNorm database. Product is deactivated and no generic equivalents are available as per Redbook.
3.	Ultresa	70	Name identified in RxNorm database. Product is deactivated and no generic equivalents are available as per Redbook.

Appendix D: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with no overlap or numerical similarity in Strength and/or Dose-N/A

Appendix E: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with overlap or numerical similarity in Strength and/or Dose

No.	**Proposed name:** Multrys **Established name:** trace elements injection **Dosage form:** injection **Strength**: Each mL contains zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg **Usual Dose:** 0.4 kg to 0.59 kg: 0.2 mL every other day. 0.6 kg to less than 10 kg: (b) (4) mL/kg/day, with a cap of 1 mL per day	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
1.	Colcrys	66	This name pair has sufficient orthographic and phonetic differences.
2.	Multaq	64	The suffixes ('trys' vs. 'taq') of the name pair have some differences. The ending of second syllables ('rys' vs. 'aq') sound different. In addition to orthographic and phonetic differences, the following product characteristics may help to minimize the risk of error: • Multrys is available as injection administered intravenously whereas Multaq is available as a tablet administered orally. There is no overlap in dosage form or route of administration (if included on a prescription/medication order). • Multaq is only indicated for adults whereas Multrys is indicated for neonates and pediatric patients weighing less than 10 kg. • Multrys will be used as an additive in TPN solutions, which in clinical practice, is considered a high-alert medication requiring special safeguards in various points of the medication use process to reduce the risk of error. Additives for TPN

No.	**Proposed name:** Multrys **Established name:** trace elements injection **Dosage form:** injection **Strength**: Each mL contains zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg **Usual Dose:** 0.4 kg to 0.59 kg: 0.2 mL every other day. 0.6 kg to less than 10 kg: (b) (4) mL/kg/day, with a cap of 1 L per day	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
			solutions are typically ordered by the established name using a TPN prescription/ order program and it is not anticipated that Multrys will be written on a medication order alone. Additionally, there are compatibility considerations with TPN solutions. When all of the aforementioned mitigations are considered in totality, we find the risk of confusion is adequately minimized in this case.
3.	(b) (4) ***	62	This name pair has sufficient orthographic and phonetic differences.
4.	Ultrasal	62	This name pair has sufficient orthographic and phonetic differences.
5.	Ultram	62	This name pair has sufficient orthographic and phonetic differences.
6.	Marpres	62	This name pair has sufficient orthographic and phonetic differences.
7.	Multitrace-4	61	The lengths of [root] names differ by three letters. The root name Multitrace has an additional syllable as compared to Multrys. The endings of the second syllables ('trys' vs.'ti') provide some phonetic differences. We note that Multitrace products have a modifier ('4 Neonatal', '4 Pediatric' or '5')

No.	**Proposed name:** Multrys **Established name:** trace elements injection **Dosage form:** injection **Strength**: Each mL contains zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg **Usual Dose:** 0.4 kg to 0.59 kg: 0.2 mL every other day. 0.6 kg to less than 10 kg: (b) (4) mL/kg/day, with a cap of 1 L per day	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
			that is absent in Multrys. Therefore, as Multitrace is not available under the root name alone, a modifier or product strength would need to be specified on a prescription/medication order. In addition to the orthographic and phonetic differences, we note that both Multrys and Multitrace products are considered high-alert medications which require safeguards at various points of the medication use process to reduce the risk of error. In clinical practice, additives for TPN solutions are typically ordered by the established names using a TPN prescription/order program and it is not anticipated that Multrys and Multitrace products will be written on a medication order alone. Therefore, in this instance, due to the abovementioned factors, we find this name pair acceptable.
8.	Multitrace-5	61	The lengths of [root] names differ by three letters. The root name Multitrace has an additional syllable as compared to Multrys. The endings of the second syllables ('trys' vs.'ti') provide some phonetic differences.

No.	**Proposed name:** Multrys **Established name:** trace elements injection **Dosage form:** injection **Strength**: Each mL contains zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg **Usual Dose:** 0.4 kg to 0.59 kg: 0.2 mL every other day. 0.6 kg to less than 10 kg: (b) (4) mL/kg/day, with a cap of 1 mL per day	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
			We note that Multitrace products have a modifier ('4 Neonatal', '4 Pediatric' or '5') that is absent in Multrys. Therefore, as Multitrace is not available under the root name alone, a modifier or product strength would need to be specified on a prescription/medication order. In addition to the orthographic and phonetic differences, we note that both Multrys and Multitrace products are considered high-alert medications which require safeguards at various points of the medication use process to reduce the risk of error. In clinical practice, additives for TPN solutions are typically ordered by the established names using a TPN prescription/order program and it is not anticipated that Multrys and Multitrace products will be written on a medication order alone. Therefore, in this instance, due to the abovementioned factors, we find this name pair acceptable. Therefore, in this instance, due to the abovementioned factors, we find this name pair acceptable.
9.	Milprosa	61	This name pair has sufficient orthographic and phonetic differences.
10.	Tums Ultra	60	This name pair has sufficient orthographic and phonetic differences.

No.	**Proposed name:** Multrys **Established name:** trace elements injection **Dosage form:** injection **Strength**: Each mL contains zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg **Usual Dose:** 0.4 kg to 0.59 kg: 0.2 mL every other day. 0.6 kg to less than 10 kg: (b) (4) mL/kg/day, with a cap of 1 mL per day	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
11.	Mulpleta	60	This name pair has sufficient orthographic and phonetic differences.
12.	Zortress	60	This name pair has sufficient orthographic and phonetic differences.
13.	Xelstrym***	59	This name pair has sufficient orthographic and phonetic differences.
14.	Ryaltris***	59	This name pair has sufficient orthographic and phonetic differences.
15.	Mytrex	58	This name pair has sufficient orthographic and phonetic differences.
16.	Valtrum	58	This name pair has sufficient orthographic and phonetic differences.
17.	Ultomiris	58	This name pair has sufficient orthographic and phonetic differences.
18.	Remular-S	58	This name pair has sufficient orthographic and phonetic differences.
19.	Mercury	56	This name pair has sufficient orthographic and phonetic differences.
20.	Ultravist	56	This name pair has sufficient orthographic and phonetic differences.
21.	Ultravist 150	56	This name pair has sufficient orthographic and phonetic differences.
22.	Ultravist 240	56	This name pair has sufficient orthographic and phonetic differences.
23.	Ultravist 300	56	This name pair has sufficient orthographic and phonetic differences.
24.	Ultravist 370	56	This name pair has sufficient orthographic and phonetic differences.

No.	**Proposed name:** Multrys **Established name:** trace elements injection **Dosage form:** injection **Strength**: Each mL contains zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg **Usual Dose:** 0.4 kg to 0.59 kg: 0.2 mL every other day. 0.6 kg to less than 10 kg: (b) (4) mL/kg/day, with a cap of 1 mL per day	POCA Score (%)	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
25.	Multigen	56	The infixes/suffixes ('trys' vs. 'tigen') of the name pair have some differences. Multigen has an additional syllable. The ending of the second syllables ('trys' vs. 'ti') sound different. In addition to orthographic and phonetic differences, the following product characteristics may help to minimize the risk of error: • Multrys is available as injection administered intravenously whereas Multigen is available as a tablet administered orally. Therefore, there is no overlap in dosage form or route of administration (if included on a prescription/ medication order). • Multigen is only indicated for adults whereas Multrys is indicated for neonates and pediatric patients weighing less than 10 kg. • Multrys will be used as an additive in TPN solutions, which in clinical practice, is considered a high-alert medication requiring special safeguards in various points of the medication use process to reduce the risk of error. Additives for TPN solutions are typically ordered by the established name using a TPN

No.	**Proposed name:** Multrys **Established name:** trace elements injection **Dosage form:** injection **Strength**: Each mL contains zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg **Usual Dose:** 0.4 kg to 0.59 kg: 0.2 mL every other day. 0.6 kg to less than 10 kg: (b) (4) mL/kg/day, with a cap of 1 mL per day	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
			prescription/ order program and it is not anticipated that Multrys will be written on a medication order alone. Additionally, there are compatibility considerations with TPN solutions. Therefore, in this instance, due to the abovementioned factors, we find this name pair acceptable.
26.	Ultracet	56	This name pair has sufficient orthographic and phonetic differences.
27.	Xelpros	56	This name pair has sufficient orthographic and phonetic differences.
28.	Miltuss EX	55	This name pair has sufficient orthographic and phonetic differences.
29.	Multihist D	55	This name pair has sufficient orthographic and phonetic differences.
30.	Zaltrap	55	This name pair has sufficient orthographic and phonetic differences.
31.	Motrin	54	The suffixes ('trys' vs. 'rin') of the name pair provide sufficient orthographic differences. The endings of the second syllables ('trys' vs.'rin') provide some differences. In addition to the orthographic and phonetic differences, the following product characteristics would help to minimize the risk of error: • Multrys is a single strength product whereas Motrin is available in different

No.	Proposed name: Multrys Established name: trace elements injection Dosage form: injection Strength: Each mL contains zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg Usual Dose: 0.4 kg to 0.59 kg: 0.2 mL every other day. 0.6 kg to less than 10 kg: (b) (4) mL/kg/day, with a cap of 1 mL per day	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
			strengths and dosage forms (tablets: 400 mg, 600 mg and 800 mg; oral suspension: 100 mg/5 mL). Therefore, a strength of Motrin would need to be specified on a prescription/ medication order, and the strengths do not overlap with the strength of Multrys. • Multrys is available as an injection administered intravenously whereas Motrin is available as a tablet and oral suspension administered orally. Furthermore, there are various over-the-counter products under the family name of 'Motrin' (e.g., Motrin IB, Motrin Migraine, Motrin PM etc.). Therefore, the dosage form for Motrin would need to be specified and there is no overlap in dosage form or route of administration (if included on a prescription/ medication order), which further differentiates this family of products from the proposed product. • Multrys will be used as an additive in TPN solutions, which in clinical practice, is considered a high-alert medication requiring special safeguards in various points of the medication use process to reduce the risk of error. Also, in clinical practice, additives for TPN solutions are

No.	Proposed name: Multrys Established name: trace elements injection Dosage form: injection Strength: Each mL contains zinc 1,000 mcg, copper 60 mcg, manganese 3 mcg, and selenium 6 mcg Usual Dose: 0.4 kg to 0.59 kg: 0.2 mL every other day. 0.6 kg to less than 10 kg: (b) (4) mL/kg/day, with a cap of 1 mL per day	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
			typically ordered by the established name using a TPN prescription/ order program and it is not anticipated that Multrys will be written on a medication order alone. Additionally, there are compatibility considerations with TPN solutions. Therefore, in this instance, due to the abovementioned factors, we find this name pair acceptable.
32.	Voltaren	50	This name pair has sufficient orthographic and phonetic differences.

Appendix F: Low Similarity Names (e.g., combined POCA score is ≤54%)

No.	Name	POCA Score (%)
1.	Emcyt	36

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described.

No.	Name	POCA Score (%)	Failure preventions
1.	Sultrin	64	Brand discontinued with no generic equivalents available. NDA 5794 withdrawn FR effective 06/16/2006.

No.	Name	POCA Score (%)	Failure preventions
2.	Metryl	63	International product formerly marketed in the south Africa per Micromedex database.
3.	Mallopress	62	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
4.	Multilex	62	Name identified i (b) (4) external study. Brand discontinued with no generic equivalents available.
5.	Maltose	62	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
6.	Mallotuss	61	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
7.	Paltrase	61	Name identified in RxNorm database. Product is deactivated and no generic equivalents are available.
8.	Meteros	58	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
9.	Milprem-200	58	Brand discontinued with no generic equivalents available. NDA 011045 withdrawn FR effective 09/29/1995.
10.	Milprem-400	58	Brand discontinued with no generic equivalents available. NDA 011045 withdrawn FR effective 09/29/1995.
11.	(b) (4);***	58	Proposed proprietary name (b) (4) **) for IND 122065 found unacceptable by DMEPA (OSE#2018-20921258 dated 04/13/2018) Subsequently, the proposed proprietary name Soaanz *** was found conditionally acceptable for NDA 213218.
12.	Trysul	56	Brand discontinued with no generic equivalents available. ANDA 087887 withdrawn FR effective 12/07/2007.
13.	Ultragris-165	56	Product discontinued with no generic equivalents available. ANDAs 062645 and 062646 withdrawn FR effective 11/12/2015
14.	Ultragris-330	56	Product discontinued with no generic equivalents available. ANDAs 062645 and 062646 withdrawn FR effective 11/12/2015

No.	Name	POCA Score (%)	Failure preventions
15.	Altresyn	56	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
16.	Molasses	55	Product is not a drug. It is a food product.
17.	Matrix	55	International product marketed in Argentina and India per Micromedex database.

Appendix H: Names not likely to be confused due to absence of attributes that are known to cause name confusion[j].

No.	Name	POCA Score (%)
1.	Butrans	60
2.	Nulibry	60
3.	(b) (4)***	58
4.	Nutr-E-Sol	57
5.	Zulresso	57
6.	Sulfatrim-SS	56
7.	Altaryl	56
8.	Kutrase	56
9.	(b) (4)***	55

[j] Shah, M, Merchant, L, Chan, I, and Taylor, K. Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

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/s/

SHERLY ABRAHAM
05/13/2021 04:05:31 PM

IDALIA E RYCHLIK
05/14/2021 11:26:05 AM

MISHALE P MISTRY
05/17/2021 05:20:16 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209376Orig1s002

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

NDA 209376/S-002

ADVICE/INFORMATION REQUEST

American Regent, Inc.
Attention: Elizabeth Ernst,
Global Executive Director of Regulatory Affairs
6610 New Albany Road East
New Albany, OH 143054

Dear Ms. Ernst,

Please refer to your supplemental new drug application (sNDA) dated and received on December 11, 2020, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for MULTRYS™ (trace elements injection 4*) Injection.

We have the following comments and information requests. We request a prompt written response by June 25, 2021 in order to continue our evaluation of your sNDA.

Based on the proposed (b) (4) acceptance criterion in the drug product specification, the maximum potential e t (b) (4) µg/kg/day) will be (b) (4) % of the maximum (b) (4) dose routinely used for total parenteral nutrition (TPN) in the target patient population (b) (4) This assessment is based on the target dose volume (b) (4) kg/day) in all weight bands for this patient population. Therefore, we request that the acceptance criterion fo (b) (4) be reduced from not more than (NMT (b) (4) µg/mL to NM (b) (4) µg/mL. This change will reduce the risk of toxicity from tota (b) (4) exposure in TPN (b) (4) (b) (4), and is supported by the batch data (b) (4) (b) (4)

If you have any questions, please contact me, Thao Vu, Regulatory Project Manager, at (240) 402-2690.

Sincerely,

{See appended electronic signature page}

Frank A. Anania, M.D., FACP, AGAF, FAASLD
Deputy Director
Division of Hepatology and Nutrition
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

FRANK A ANANIA
06/25/2021 07:56:31 AM

From: Vu, Thao
To: Ernst, Elizabeth
Subject: NDA 209376/S-00 (b) (4) S-002 -Carton and Container 6.1.21
Date: Tuesday, June 1, 2021 4:52:00 PM
Attachments: image002.png

Dear Liz,

Below are recommendations regarding the Carton and Container labels from medication error's perspective. Please review and submit by COB Thursday.

Please confirm receipt and let me know if you have additional questions or concerns.

APPEARS THIS WAY ON ORIGINAL

Table 1. Identified issues and Recommendations			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label and Carton Labeling			
1.	The strength statement continues to lack prominence.	21 CFR 201.15(a)(6)	Increase the prominence of the strength statement. Box the product strength statement: "Each mL (b) (4)
2.	As currently displayed, the net quantity statement is more prominent than the product strength statement.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is more prominent.	Decrease the prominence of net quantity statement; consider un-bolding the net quantity statement. Ensure that the net quantity statement does not compete for prominence with the product strength statement.
3.	Lack of clarity in package type and product handling instruction.	If the vial contains more drug than needed to provide the dose listed in the Dosage and Administration section of the PI, than the "Discard Unused Portion" statement should appear after the 'single-dose vial' statement to help mitigate drug use errors.	Consider re-aligning the "Single-Dose Vial" and "Discard Unused Portion" statements to read: "Single-Dose Vial – Discard Unused Portion" to minimize risk of the entire contents of the vial being given as a single dose.

Regards,
Thao

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/s/

THAO M VU
06/01/2021 04:56:56 PM

NDA 209376/S-002

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

American Regent, Inc.
6610 New Albany Road East
New Albany, OH 43054

ATTENTION: Elizabeth Ernst
Global Executive Director of Regulatory Affairs

Dear Ms. Ernst:

Please refer to your supplemental new drug application (sNDA) dated and received December 11, 2020, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Trace Elements Injection.

We also refer to your correspondence, dated and received March 17, 2021, requesting review of your proposed proprietary name, Multrys.

We have completed our review of the proposed proprietary name, Multrys and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your March 17, 2021, submission are altered prior to approval of the supplemental marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*[1]

- *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022*[2]

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4952. For any other information regarding this application, contact Thao Vu, Regulatory Project Manager in the Office of New Drugs, at (240) 402-2690.

Sincerely,

{See appended electronic signature page}

Danielle Harris, PharmD
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS
05/20/2021 08:53:43 AM

From: Vu, Thao
To: Ernst, Elizabeth
Subject: NDA 209376/S-00 (b) (4) S-002 -PI dated 5.6.21
Date: Thursday, May 6, 2021 8:07:00 AM
Attachments: 209376-S-002 Multrys PI dated 5.6.21.docx
image001.png
Importance: High

Dear Liz,

Attached is the PI dated 5.6.21 for your review and submit by COB 5.13.21. Please confirm receipt and let me know if you have additional questions or concerns upon reviewing.

Regards,

Thao M. Vu, R.Ph
Regulatory Project Manager

Hepatology and Nutrition
Division of Regulatory Operations for Immunology & Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Rm 5232
Silver Spring, MD 20993
Office: 240-402-2690
Fax: **301.837.6415**
Email: thao.vu@fda.hhs.gov

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/s/

THAO M VU
05/13/2021 04:40:34 PM

From: Vu, Thao
To: Ernst, Elizabeth
Subject: NDA 209376/S-00 (b) (4) S-002 -Carton and Container 5.13.21
Date: Thursday, May 13, 2021 4:35:00 PM

Dear Liz,

Below are the recommendations regarding the Carton and Container labels from medication error's perspective. Please review and submit by COB Tuesday.

Please confirm receipt and let me know if you have additional questions or concerns.

Table 2. Identified Issues and Recommendations for American Regent, Inc.

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The established name is not at least half the size of the proprietary name.	21 CFR 201.10(g)(2).	Revise the established name to be at least half the size of the proprietary name.
2.	The strength statement lacks prominence.	21 CFR 201.15(a)(6)	Increase the prominence of the strength statement.
3. To be	The net quantity statement is more prominent than the product strength statement and is located in close proximity to the product strength statement.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is more prominent and located in close proximity to the strength statement.	Decrease the prominence and relocate the net quantity statement away from the product strength, such as to the bottom corner of the principal display panel.

4.	The route of administration statement is misleading and may be improved to improve clarity.	We recommend this to minimize the risk of administering the drug as an intravenous bolus.	Consider revising the statemen (b) (4)r (b) (4) (b) (4)" to "For intravenous infusion after dilution and admixing".
5.	The package type term, single-dose vial, is overtly prominent and the sentence "**discard unused portion**" is bolded.	Unnecessary prominence of package type term and discard statement takes the reader's attention away from other important information on the PDP such as the established name, dosage form statement and strength statement.	Revise the package type term by decreasing the font size and unbold the sentence, "discard unused portion".
Container Label			
1.	The usual dose statement is absent on the container label.	As per 21 CFR 201.55, the usual dose statement is required on the container label.	Add the usual dose statement, "Recommended Dosage: See prescribing information."
Carton Labeling			
1.	It is unclear where the machine-readable product identifier is located on the label. Additionally, the format of the	The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable	The DSCSA guidance on product identifiers recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier. Include the machine-readable data matrix barcode and a human readable product identifier to the carton labeling. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the

	human-readable portion of the product identifier is not identified.	and machine-readable (2D data matrix barcode) product identifier.	following: **NDC: [insert NDC]** **SERIAL: [insert serial number]** **LOT: [insert lot number]** **EXP: [insert expiration date]** We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

Regards,
Thao

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/s/

THAO M VU
05/13/2021 04:38:13 PM

NDA 209376/S-002

PROPRIETARY NAME ACKNOWLEDGEMENT

American Regent, Inc.
6610 New Albany Road East
New Albany, OH 43054

ATTENTION: Elizabeth Ernst
Global Executive Director of Regulatory Affairs

Dear Ms. Ernst:

Please refer to your supplemental new drug application (sNDA) dated and received December 11, 2020, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Trace Elements Injection 4*, USP.

We acknowledge receipt of your correspondence, dated and received March 17, 2021, requesting a review of your proposed proprietary name, Multrys.

Therefore, the user fee goal date to review your request for proprietary name is June 15, 2021.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me at (301) 796-4952. For any other information regarding this application, contact Thao M. Vu, Regulatory Project Manager, in the Office of New Drugs at (240) 402-2690.

Sincerely,

{See appended electronic signature page}

Shawnetta Jackson, MS, GWCPM
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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/s/

SHAWNETTA M JACKSON
04/07/2021 11:46:05 PM

NDA 209376/S-002

PROPRIETARY NAME REQUEST WITHDRAWN

American Regent, Inc.
6610 New Albany Road East
New Albany, OH 43054

ATTENTION: Elizabeth Ernst
Global Executive Director of Regulatory Affairs

Dear Ms. Ernst:

Please refer to your supplemental new drug application (sNDA) dated and received December 11, 2020, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Trace Elements Injection 4*, USP.

We also refer to:

- Your correspondence, dated and received January 5, 2021, requesting review of your proposed proprietary name, (b) (4)
- The teleconference held between the Agency and American Regent, Inc. on March 12, 2021, to discuss the Agency's preliminary findings and regulatory options for your proposed proprietary name (b) (4).
- Your correspondence, dated and received on March 16, 2021, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4).

The proprietary name request is considered withdrawn as of March 16, 2021.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted. (See the guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names*[1] and PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022[2].

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me at (301) 796-4952. For any other information regarding this application, contact Thao Vu, Regulatory Project Manager in the Office of New Drugs, at (240) 402-2690.

Sincerely,

{See appended electronic signature page}

Shawnetta Jackson, MS
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

SHAWNETTA M JACKSON
03/29/2021 04:52:05 PM

TELECONFERENCE MEETING MINUTES

Meeting Date	Friday, March 12, 2021
Time:	11:30 AM to 12 PM
Meeting Location:	Webex
Application Number:	NDA 209376/S-002
Product Name and Strength:	(b) (4) Zinc 1mg, copper 0.06 mg, manganese 3 mcg, and selenium 6 mcg per mL
Applicant/Sponsor Name:	American Regent
Call-In Information:	800.504.8071 Passcode (b) (4)
Meeting Chair:	Mishale Mistry, Pharm.D., MPH, DMEPA Associate Director for Nomenclature and Labeling
FDA Participants:	<u>Division of Medication Error Prevention and Analysis (DMEPA)</u> Sherly Abraham, R.Ph., Safety Evaluator Idalia E. Rychlik, Pharm.D., Team Leader Mishale Mistry, Pharm.D., MPH, Associate Director for Nomenclature and Labeling <u>Office of Surveillance and Epidemiology (OSE)</u> Shawnetta Jackson, M.S., Safety Regulatory Project Manager Aleksander Winiarski, Pharm.D., Safety Regulatory Project Manager Team Leader <u>Office of New Drugs (OND)</u> Thao Vu, DHN Project Manager Frank Anania, DHN Deputy Director Ashish Dhawan, DHN Medical Officer Fanti Paolo, DHN Lead Medical Officer (Acting) Judy Racoosin, DHN Deputy Director for Safety Elizabeth Shang, DHN Associate Director for Labeling (Acting) Mona Khurana, DPMH Lead Medical Officer Ramy Abdelrahman, DPMH Medical Officer Meshaun Payne, DPMH RPM

Office of Pediatric Therapeutics (OPT)/Office of the Commissioner
Gerri Baer, Neonatology Team Leader
An Massaro, Neonatology Medical Officer

Sponsor Participants:
Dr. Linda Mundy, VP & Chief Medical Officer
Dr. Gopal Anyarambhatla, VP & Chief Scientific Officer
Dr. Anthony DiGuglielmo, Sr. Director, Head of Pharmacovigilance
Richard Lawrence, Director of R&D
Dr. Syed Numan, Medical Director and Head of Medical Affairs
Amy Epperly, Regulatory Manager
Gennine Kelly, Sr. Director Marketing and Portfolio Management
Elizabeth Ernst, Global Regulatory Executive Director
(b) (6) MS, RD, CNSC, Consultant for ARI

MEETING OBJECTIVES
The purpose of this teleconference is to notify American Regent of our preliminary findings for the proposed proprietary name (b) (4)

BACKGROUND
American Regent submitted a Request for Proprietary Name Review on Tuesday, January 5, 2021, to review the proposed proprietary name (b) (4)

DMEPA CONCERNS WITH THE PROPOSED PROPRIETARY NAME
We requested this teleconference to notify you of our preliminary safety concerns with your proposed proprietary name (b) (4) submitted under NDA 209376/S-002.

1. **Propose** (b) (4)
   - We note that you propose (b) (4) to distinguish the proposed formulation of Tralement, which is indicated for neonates and infants weighing less than 10 kg, from the currently marketed product which is indicated for adults and pediatric patients weighing 10 kg or more.
   - We note tha (b) (4) Therefore, we are concerne (b) (4) which may have adverse clinical outcomes given that the approved Tralement rmulation does not provide appropriate dosing for pediatric patients less than 10 kg.

(b) (4)

2. **Use o** [redacted]
   - Furthermore, post marketing experience shows tha [redacted] resulting in wrong drug medication errors.[2]
   - We are concerned [redacted]
   - We note that both the currently approved Tralement and the proposed product contain the same active ingredients in different concentrations, are single-strength products, and are dosed based on weight. We note that the recommended dosing between the two formulations may overlap which can further contribute to the risk of wrong drug errors. For example, the recommended dose o [redacted] for patients weighing less tha [redacted] kg i [redacted] mL/kg/day with a maximum dose of 1 mL per day. The recommended dosage of Tralement for pediatric patients weighing at least 50 kg and adults patients is also 1 mL per day. Therefore, if a healthcare provider prescribes [redacted] for an infant weighin [redacted] kg an [redacted] This medication error would lead to excessive dosing in the infant which could be associated with adverse clinical outcomes.

REGULATORY OPTIONS FOR THE PROPOSED PROPRIETARY NAME

Given the above noted concerns, we wanted to present you with the following regulatory options:

1. You may withdraw the proprietary name request for the proposed proprietary name, [redacted] for pediatric patients less than 10 kg to clearly distinguish it from currently marketed Tralement product.
2. Alternatively, you may withdraw the proprietary name request for the proposed proprietary name [redacted] given the product's proposed indication. If you decide to proceed with this option, we recommend that you clearly describe in your submission your specific risk mitigation strategies to address the clinical concern [redacted]
3. Wait to receive a decisional letter from us.

As your PDUFA goal date is April 5, 2021, we would recommend informing us of your decision as soon as possible.

[2] Lesar TS. Prescribing errors involving medication dosage forms. J Gen Intern Med. 2002 Aug;17(8):579-87.

DISCUSSION (IF ANY)

Discussion of risk mitigation that sponsor considered internally such as, total parenteral nutrition (TPN) order sets as standards of pharmacy practice throughout the majority of major medical centers and TPN is template driven when ordered from a hospital.

Discussion o (b) (4) and clarification of medication error concerns and regulatory options presented.

NEXT STEPS/ACTION ITEMS

Sponsor to provide their decision by close of business Tuesday March 16, 2021.

Sponsor confirmed via email correspondence on March 16, 2021, that they plan to submit withdrawal of the proposed proprietary name (b) (4) and will submit a new name.

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/s/

SHAWNETTA M JACKSON
03/23/2021 04:20:50 PM

U.S. FOOD & DRUG ADMINISTRATION

NDA 209376/S-002

INFORMATION REQUEST

American Regent, Inc.
Attention: Elizabeth Ernst,
Global Executive Director of Regulatory Affairs
6610 New Albany Road East
New Albany, OH 143054

Dear Ms. Ernst,

Please refer to your supplemental new drug application (sNDA) dated and received on December 11, 2020, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tralement (trace elements injection 4*) Injection.

We have the following comments and information requests. We request a prompt written response by March 15, 2021 in order to continue our evaluation of your sNDA.

Pertinent to the dosing of the pediatric formulation of Tralement in neonates and infants weighing < 10 kg, we note that the currently proposed labeling instructions:

1. Do not include the smallest preterm neonates, i.e., those with body weight < 0.5 kg;
2. (b) (4) (b) (4) is not aligned with subsection 2.5 (Recommended Dosage in Adults and Pediatric Patients and Monitoring Considerations) of labeling for the currently approved Tralement formulation that states "Accumulation of manganese in the brain can occur with long-term administration with higher than the recommended dosage of 1 mcg/kg/day…".

Based on the above, we ask you to provide:

1. A proposal for the formulation that you submitted that revises the labeling instructions to include neonatal body weights down to 0.4 kg and any risk mitigation efforts to reduce medication errors associated with dosing instructions in the lowest neonatal body weights; and

2. A discussion of the feasibility of modifying the (b) (4) pediatric formulation of Tralement by reformulating the produc (b) (4)

(b) (4)

If you have any questions, please contact me, Thao Vu, Regulatory Project Manager, at (240) 402-2690.

Sincerely,

{See appended electronic signature page}

Thao M. Vu, R.Ph
Regulatory Health Project Manager
Hepatology and Nutrition
Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

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/s/

THAO M VU
03/08/2021 03:42:33 PM

From: Vu, Thao
To: "Ernst, Elizabeth"
Subject: NDA 209376/S-00 (b) (4) IR dated 1.27.21
Date: Wednesday, January 27, 2021 10:22:00 AM
Attachments: image001.png
Importance: High

Dear Liz,

We are reviewing (b) (4) S-002 and have the following information request:

Please refer to the report titled: *"RISK ASSESSMENT SUMMARY FOR POTENTIAL ELEMENTAL IMPURITIES IN* (b) (4) *(TRACE ELEMENTS INJECTION 4*, USP)"*. The data table containing the measurements of elemental impurities indicates that the drug product samples were not tested fo (b) (4) We note the report provides the following explanation for this issue:

- *"The final risk assessment will be performed once NMR method validation fo* (b) (4) *is completed and the three exhibit batches are tested for* (b) (4)
- Please submit th (b) (4) data as soon as possible. If you do not expect this data will be available for submission by February 12, 2021, please inform us immediately of the earliest expected date of submission.

Please confirm receipt and let me know if you have additional questions or concerns.

Regards,

Thao M. Vu, R.Ph
Regulatory Project Manager

Hepatology and Nutrition
Division of Regulatory Operations for Immunology & Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Rm 5232
Silver Spring, MD 20993
Office: 240-402-2690
Fax: **301.837.6415**
Email: thao.vu@fda.hhs.gov

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/s/

THAO M VU
01/27/2021 10:27:53 AM

NDA 209376/ S-002

PROPRIETARY NAME ACKNOWLEDGEMENT

American Regent, Inc.
6610 New Albany Road East
New Albany, OH 43054

ATTENTION: Elizabeth Ernst
Global Executive Director of Regulatory Affairs

Dear Ms. Ernst:

Please refer to your supplemental new drug application (sNDA) dated and received December 11, 2020, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Trace Elements Injection 4*, USP.

We acknowledge receipt of your correspondence, dated and received January 5, 2021, requesting a review of your proposed proprietary name [redacted] (b) (4)

If the application is filed, the user fee goal date to review your request for proprietary name is April 5, 2021.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me at (301) 796-4952. For any other information regarding this application, contact Thao M. Vu, Regulatory Project Manager, in the Office of New Drugs at (240) 402-2690.

Sincerely,

{See appended electronic signature page}

Shawnetta Jackson, MS, GWCPM
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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/s/

SHAWNETTA M JACKSON
01/12/2021 02:51:41 PM

NDA 209376/S-002

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

American Regent, Inc.
Attention: Elizabeth Ernst
Global Executive Director of Regulatory Affairs
6610 New Albany Road East
New Albany, OH 143054

Dear Ms. Ernst,

We have received your supplemental new drug application (sNDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 209376

SUPPLEMENT NUMBER: S-002

PRODUCT NAME: (b) (4) (trace elements injection 4*)

DATE OF SUBMISSION: December 11, 2020

DATE OF RECEIPT: December 11, 2020

This supplemental application proposes for the addition of a new strength (1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 9, 2021, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be April 11, 2021.

If you have questions, call me, at (240) 402-2690.

Sincerely,

{See appended electronic signature page}

Thao M. Vu, R.Ph
Regulatory Health Project Manager
Hepatology and Nutrition
Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

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/s/

THAO M VU
01/04/2021 01:56:00 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR NEONATAL-PERINATAL MEDICINE CONSULTATION

Send to:
Gerri Baer, MD
Neonatology Team Leader
Office of Pediatric Therapeutics
10903 New Hampshire Avenue, WO32-5154
Silver Spring, MD 20993-0002
Tel: (240) 402-2865; Fax (301) 847-8619
Email: gerri.baer@fda.hhs.gov

FROM:
Center: CDER
Division: OND/OII/DHN
Requesting Reviewer Name/Email:
RPM/CSO Name/Email: Thao Vu, thao.vu@fda.hhs.gov

DATE	IND/BLA/IDE NO.	NDA//510(K)/PMA NO.	
12/16/2020		NDA 209376/S-002	
PRODUCT NAME:	**PRIORITY CONSIDERATION**	**PRODUCT CLASSIFICATION**	**DESIRED COMPLETION DATE**
(b) (4) (trace elements injection 4*)	Standard	LVP	2/11/2021

SPONSOR: American Regents INC

PHASE OF PRODUCT DEVELOPMENT

☐ NONCLINICAL ☐ CLINICAL PHASE: ☐ 1 ☐ 2 ☐ 3 ☐ 4

REASON FOR REQUEST

☐ NEW PROTOCOL, SUBMITTED TO (**CHOOSE ONE**):
- ☐ NEW IND, 30 DAY SAFETY DATE:
- ☐ ACTIVE IND, Study Start Date, if known:

☐ NEW CORRESPONDENCE
☐ CLINICAL HOLD
☐ RESUBMISSION
☐ SAFETY/EFFICACY **(please explain below)**

☐ MEETING
- ☐ PreIND
- ☐ End of Phase II
- ☐ Internal
- ☐ Sponsor
- ☐ AC Planning

☐ RESPONSE TO DEFICIENCY LETTER
☐ LABELING REVISION
☐ GUIDANCE DEVELOPMENT
☐ INSPECTION REPORT
☐ SUBJECT OF ADVISORY COMMITTEE MEETING
☒ OTHER (**SPECIFY BELOW**):

SUPPORTING INFORMATION FOR CONSULT
(please provide electronic copy if possible)

☐ PROTOCOL	☐ INVESTIGATOR'S BROCHURE
☐ MEDICAL OFFICIER'S REVIEW(S)	☐ SUPERVISOR'S REVIEW
☐ INFORMED CONSENT DOCUMENTS	☒ OTHER CONSULTATIONS
☐ MEETING PACKAGE	☐ PEER REVIEW ARTICLES

SPECIFIC QUESTION(S) TO BE ADDRESSED

1.
2.
3.
4.
5.

COMMENTS/SPECIAL INSTRUCTIONS:

NDA 209376 for Tralement was approved on 7/2/2020 indicated in adult and pediatric patients weighing at least 10 kg, as a source of zinc, copper, manganese, and selenium. Formulation approved in the NDA was 3 mg Zn/mL, 0.3 mg Cu/mL, 55 µg Mn/mL, and 60 µg Se/mL. With this approval, the DHN issued a PREA PMR 3877-02: to develop a weight-appropriate formulation for pediatric patients weighing less than 10 kilograms. The Applicant submitted S-002 on 12/11/2020 proposed to add a new formulation, (1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL) and to fulfill the PREA PMR requirements.

DHN requests OPT's assistance to review and determine the appropriate dosing to support the neonatal population.

View EDR: View submission in docuBridge
Cover Letter: \\CDSESUB1\evsprod\NDA209376\0050\m1\us\12-cover-letters\cover-letter-2020-12-11-s0050-neonate-pas.pdf
EDR Location: \\CDSESUB1\evsprod\NDA209376\0050

Sharepoint 209376-S-00 (b) (4) received 12.11.20

Previous OPT consult for NDA 209376(dated 04/24/2020)

SIGNATURE OF REQUESTER Thao Vu, R.Ph., RPM/DHN	METHOD OF DELIVERY (Check one) ● EMAIL ☐ INTER-OFFICE
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

THAO M VU
12/18/2020 11:45:54 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
OSE-DMEPA

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Thao Vu, RPM, OII/ORO/DHN, 240-402-2690

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12/16/2020		NDA 209376/S-002	PAS supplement	12/11/2020

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
12/11/2020	Standard	LVP	2/11/2021

NAME OF FIRM: American Regents INC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☒ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

NDA 209376 for Tralement was approved on 7/2/2020 indicated in adult and pediatric patients weighing at least 10 kg, as a source of zinc, copper, manganese, and selenium. Formulation approved in the NDA was 3 mg Zn/mL, 0.3 mg Cu/mL, 55 µg Mn/mL, and 60 µg Se/mL. With this approval, the DHN issued a PREA PMR 3877-02: to develop a weight-appropriate formulation for pediatric patients weighing less than 10 kilograms. The Applicant submitted S-002 on 12/11/2020 proposing to add a new formulation, (1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL) and to fulfill the PREA PMR requirements.

- DHN is requesting DMEPA to review all aspects of Labeling: PI, Carton and Container

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check all that apply)
Thao Vu, R.Ph., RPM/DHN	☒ DARRTS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

THAO M VU
12/18/2020 11:42:33 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**DIVISION OF PEDIATRIC AND MATERNAL HEALTH REQUEST FOR CONSULTATION**	
TO: CDER Division of Pediatric and Maternal Health *(please check appropriate box(es))* ☒ Pediatric Team ☐ Maternal Health Team			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Thao Vu, RPM, OND/OII/ORO/DHN, 240-402-2690	
DATE OF CONSULT 12/16/2020	IND NO.	NDA/BLA/ANDA NO. NDA 209376/S-002	TYPE OF SUBMISSION PAS supplement	DATE OF SUBMISSION 12/11/2020
NAME OF DRUG 12/11/2020	NAME OF FIRM American Regents INC		DRUG CLASS LVP	INDICATION(S) in neonatal and pediatric patients weighing less than 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.
PDUFA/BsUFA Goal Date 4/11/2021	**DPMH will work with you to establish a suitable due date for the completed consult. Please check one of the three boxes.**			
	☐ Urgent* (< 14 days)	☐ Priority (14-29 days)	☒ Routine (1 – 10 months)	

*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from DPMH team leaders.

REASON FOR REQUEST (check all that apply)

Pediatrics:	Maternal Health Team:
☐ Labeling Review – non-PLLR ☐ Safety Labeling Supplement ☐ 505(b)(2)/ANDA Pediatric Labeling ☐ Industry Meeting Attendance (PDUFA or BSUFA) ☐ Other Industry Meeting Attendance ☐ BPCA-Related Questions or Documents for Review ☒ PREA-Related Questions or Documents for Review ☐ PeRC Preparation Assistance/iPSP Review ☐ SPA ☐ 30-day IND Review ☐ Other Protocol Review ☐ Tracked Safety Issue ☐ Advisory Committee Preparation ☐ Assistance with Guidance development ☐ Assistance with Citizen Petition Response ☐ Medical Necessity Determination ☐ Off-Patent BPCA/409i Related Questions ☐ Other (please explain):	☐ Labeling Review – PLLR ☐ Labeling Review – non-PLLR ☐ Industry Meeting Attendance ☐ Pregnancy Exposure Registry (protocol or report) ☐ 30-day IND Review ☐ Evaluation of possible safety signal ☐ Risk Management – Pregnancy Prevention and Planning ☐ Clinical Lactation Study (protocol or report) ☐ Pregnancy PK (protocol or report) ☐ Guidance development ☐ Advisory Committee Preparation ☐ Citizen Petition ☐ Other (please explain):
Link to electronic submission (if available): View EDR: View submission in docuBridge Cover Letter: \\CDSESUB1\evsprod\NDA209376\0050\m1\us\12-cover-letters\cover-letter-2020-12-11-s0050-neonate-pas.pdf EDR Location: \\CDSESUB1\evsprod\NDA209376\0050	Materials to be reviewed: Sharepoint 209376-S-00 (b) (4) received 12.11.20

Version: 10/01/2017

1. Please briefly describe the submission:
NDA 209376 for Tralement was approved on 7/2/2020 indicated in adult and pediatric patients weighing at least 10 kg, as a source of zinc, copper, manganese, and selenium. Formulation approved in the NDA was 3 mg Zn/mL, 0.3 mg Cu/mL, 55 µg Mn/mL, and 60 µg Se/mL. With this approval, the DHN issued a PREA PMR 3877-02: to develop a weight-appropriate formulation for pediatric patients weighing less than 10 kilograms. The Applicant submitted S-002 on 12/11/2020 proposing to add a new formulation, (1000 µg Zn/mL, 60 µg Cu/mL, 3 µg Mn/mL, and 6 µg Se/mL) and to fulfill the PREA PMR requirements.

2. Describe the reason for your consult. Include specific questions:
- Review and determine the appropriate dosing for pediatric patients weighing less than 10kg and to fulfill the PREA PMR

3. Meeting dates requiring DPMH presence:
- Team meeting: TBD

4. Please list any prior Pediatric or Maternal Health consults for this product by date within the last 3 years that may be relevant to this consult (DARRTS Reference ID # if known):

DPMH Consult for NDA 209376(dated 02/06/2020)1

Review team:
Project Manager: Thao Vu, R.Ph.

PRINTED NAME or SIGNATURE OF REQUESTOR:
Thao Vu, R.Ph., RPM, OND/OII/ORO/DHN

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/s/

THAO M VU
12/18/2020 11:44:13 AM