Summary Report

Manganese chloride

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 5U01FD005946-06

Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

October 2021

This report was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling $2,342,364, with 100 percent funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the U.S. Government.

Table of Contents

Table of Tables

Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
ASHP	American Society of Health-System Pharmacists
ASPEN	American Society of Parenteral and Enteral Nutrition
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GI	Gastrointestinal
IRB	Institutional Review Board
IV	Intravenous
MRI	Magnetic resonance image
OTC	Over-the-counter
PN	Parenteral nutrition
ROA	Route of administration
SME	Subject matter expert
TPN	Total parenteral nutrition
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of manganese chloride (UNII code: QQE170PANO), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how manganese chloride is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how manganese chloride has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of manganese chloride and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Manganese chloride was nominated for inclusion on the 503B Bulks List by Rebecca Mitchell and Specialty Sterile Pharmaceutical Society. Manganese chloride was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Manganese chloride was nominated for nutritional supplementation via intravenous (IV) solution.

Nominators did not provide references from published peer-reviewed literature to describe the pharmacology and support the clinical use of manganese chloride.

Reasons provided for nomination to the 503B Bulks List included:

- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes and/or final product containers for administration.
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical size batch for outsourcing facilities; a single vessel compounded from bulk API is safer and more efficient than unmanageable amounts of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100 percent potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- In order to utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.
- Manufacturer backorder.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of manganese chloride products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory

agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for manganese chloride; name variations of manganese chloride were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing manganese chloride. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Manganese chloride is currently available as an FDA-approved injectable solution. The nominated products did not differ substantially from the commercially available product. Therefore, a systematic literature review was not conducted.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances manganese chloride was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify medical specialties that would potentially use manganese chloride. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

In addition to interviews with individual SMEs, a roundtable discussion with pharmacists was held. Participants were identified through outreach to professional associations that would potentially purchase compounded products from outsourcing facilities. A prequestionnaire was distributed to those who agreed to participate to collect information about the types of facilities at which participants worked and the products they purchased from outsourcing facilities (refer to Appendix 2 for complete survey and Results of survey section for results of prequestionnaire). The roundtable lasted 60 minutes and was conducted via Zoom, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

Survey

A survey was distributed to the members of professional medical associations to determine the use of manganese chloride in clinical practice. The online survey was created using Qualtrics® software (refer

to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Years 1 and 2 were not contacted to distribute the project Year 3 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Manganese chloride is available as an FDA-approved product in the nominated dosage form and ROA. Manganese sulfate is available in combination with cupric sulfate, selenious acid and zinc sulfate as an IV solution (Tralement®).
- Manganese chloride is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for manganese chloride.
- Manganese chloride is available in the nominated dosage form and ROA in Australia, Belgium, Canada, Hong Kong, Ireland, and Latvia.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date
Manganese chloride	EQ 0.1 mg/mL	Injectable	Injection	Prescription	6/26/1986

[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

Table 2. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Manganese chloride / Chromic chloride / Cupric chloride	740 mcg/mL / 22 mcg/mL / 560 mcg/mL	Solution	Intravenous	Australia	Not scheduled	10/14/1991
Manganese chloride / Copper chloride / Potassium iodide / Sodium fluoride / Sodium selenite / Zinc chloride	3.6 mcg/mL / 53.7 mcg/mL / 1.31 mcg/mL / 126 mcg/mL / 6.66 mcg/mL / 0.52 mg/mL	Solution	Intravenous	Belgium	Prescription	2/10/1997
				Hong Kong	Prescription	7/18/1995
				Latvia	Prescription	10/24/2003
	4.38 mcg/10 mL / 126 mcg/10 mL / 521 mcg/10 mL / 53.7 mcg/10 mL / 3.6 mcg/10 mL / 1.31 mcg/10 mL			Ireland	Prescription non-renewable	11/13/1995

Manganese chloride / Chromic chloride / Copper (cupric) chloride / Ferric (ferrous) chloride / Potassium iodide / Sodium fluoride / Sodium molybdate / Sodium selenite / Zinc chloride	–	Solution	Intravenous	Hong Kong	Prescription	8/11/1992
	55 mcg/10 mL / 10 mcg/10 mL / 380 mcg/10 mL / 1100 mcg/10ml / 130 mcg/10ml / 950 mcg/10ml / 19 mcg/10 mL / 79mcg/10ml / 5000 mcg/10 mL			Canada	Ethical	12/1/2020
	99 mcg/10 mL / 5.33 mcg/10 mL / 340 mcg/10 mL / 540 mcg/10 mL / 16.6 mcg/10 mL / 210 mcg/10 mL / 4.85 mcg/10 mL / 6.9 mcg/10 mL / 1.36 mg/10 mL			Ireland	Prescription non-renewable	5/16/1988
	197.9 mcg/mL / 5.3 mcg/mL / 204.6 mcg/mL / 695.8 mcg/mL / 16.6 mcg/mL / 126 mcg/mL / 2.42 mcg/mL / 7.89 mcg/mL / 681.5 mcg/mL			Belgium	Prescription	2/4/2001
	19.8 mcg/mL / 5.33 mcg/mL / 100 mcg/mL / 540 mcg/mL / 16.6 mcg/mL / 210 mcg/mL / 4.85 mcg/mL / 17.3 mcg/mL / 1050 mcg/mL			Australia	Not scheduled	7/29/2016
				Belgium	Prescription	2/3/2015
				Hong Kong	Prescription	3/10/2016
				Latvia	Prescription	4/16/2014

Abbreviation: "– ", not mentioned.

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

[c]Pharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Results of literature review

No literature review was conducted.

Pharmacology and historical use

Several studies were identified that provided valuable information about the pharmacology and historical use of manganese.

Manganese is an essential metal that is a component of metalloenzymes, primarily in mitochondria, throughout the body, where it plays a role in immune function, energy metabolism, bone mineralization, coagulation and hemostasis, and removing byproducts of oxidative stress.[6-8] Manganese sulfate and manganese chloride are both soluble in water and alcohol, but manganese chloride has better solubility in water.[8] The primary source of manganese in healthy humans is food, with intake varying amongst individual depending on diet.[8] Nuts, grains and cereals provide the highest amount of manganese while fruits, vegetables, meat, poultry and eggs provide a lower amount. When manganese is consumed orally, 3-5% is absorbed through the gastrointestinal (GI) tract. Age affects manganese absorption, with GI absorption greater in neonates and children. Diet may also affect manganese absorption, with fiber, phytates and iron reducing GI absorption.[8,9] Manganese is eliminated from the body via biliary excretion; more than 90% of manganese is excreted in bile.[9] In 2001, the Food and Nutrition Board (FNB) at the National Academies of Sciences, Engineering, and Medicine determined that there was insufficient evidence to generate an estimated average requirement (EAR) for manganese. Therefore, the FNB established an adequate intake (AI) level for all ages. The AI for manganese for adult males is 2.3 mg per day and for adult females is 1.8 mg per day.[10] Manganese deficiency is "exceptionally rare" and there have been "virtually no published reports" of manganese deficiency in nonexperimental settings.[9,11] One case report from 1992 described manganese deficiency in a child with short bowel syndrome receiving long-term parenteral nutrition (PN), which resolved with oral manganese supplementation.[12] In a review of manganese in PN, Hardy et al stated that "despite being classified as an essential trace element, there is very little evidence of Mn [manganese] deficiency being clinically relevant."[13] In animal models of manganese deficiency, impaired growth and bone formation, birth defects, disrupted carbohydrate and lipid metabolism and decreased fertility have been reported, while in humans experimentally induced manganese deficiency has resulted in dermatitis, mood alterations and hypocholesterolemia.[13,14]

Manganese toxicity (manganism) has been more commonly recognized and thoroughly described in the clinical literature than manganese deficiency. The most common etiologies of manganese toxicity are long-term total parenteral nutrition (TPN), contaminated well water, and occupational exposure.[6] Manganism is primarily a neurotoxic condition with psychiatric signs including personality change, anxiety, depression, hallucinations and psychosis, and neurological symptoms such as tremors, altered gait, memory loss, headaches and seizures.[6,8,14] Some of these neurological symptoms resemble those seen in patients with Parkinson's disease.[8]

In the 1990s, concern over reports of neurotoxicity in children due to excessive manganese led to the recommendation to decrease manganese in parenteral formulations.[15] Guidelines for parenteral trace element requirements have changed over time. In 1979, the Nutrition Advisory Group of the American Medical Association (NAG-AMA) published guidelines for parenteral trace elements, recommending manganese 150-800 mcg per day for adults.[15] The publication of these guidelines led pharmaceutical companies to manufacture sterile solutions of chromium, copper, manganese, and zinc (parenteral solutions of the other trace elements, cobalt, iodine and iron, were already

available).[15,16] In 1982, the American Medical Association and The New York Academy of Medicine held a second working conference on parenteral trace elements to review certain trace minerals, including manganese.[16] The parenteral manganese recommendation that emerged from this conference was 400-800 mcg per day for adults.[15] In 1988, the American Society for Clinical Nutrition Committee on Clinical Practice Issues recommended that stable infants and children on long-term PN receive a multi-trace element solution with zinc, copper, selenium, manganese, molybdenum, chromium, and iodine.[15] In 1994, the 9th edition of *Modern Nutrition in Health and Disease* recommended a parenteral manganese dose of 60-100 mcg per day for adults. This same dose was recommended in the American Society of Parenteral and Enteral Nutrition (ASPEN) safe practices for parenteral nutrition formulations in 1998 and again in 2004.[17,18]

In 2009, a group of scientists convened the Micronutrient Workshop to reconsider recommendations and suggest research priorities for micronutrients, including manganese, in PN. The expert who summarized the findings for manganese concluded that "The scarcity of PN-associated Mn [manganese] deficiency, plus the growing evidence for Mn toxicity, leads to the conclusion that it is unnecessary for Mn to be prescribed routinely for pediatric or long-term PN patients."[9] This expert also noted that "supplementation with fixed formulations of TE [trace element] additives can lead to potentially toxic levels of Mn [manganese],"[9] citing a 2007 study that measured trace elements in the autopsy tissues of 8 short bowel patients who had been on home PN for an average of 14 years.[19] A multi-trace element mixture containing zinc, copper, manganese, chromium, and selenium had been added to the PN of these patients for a total daily manganese dose of 700 mcg. The authors of this study found "major" elevations of manganese in liver and kidney tissues, particularly in patients with liver and kidney disease.[19] None of the patients had displayed the Parkinson's-like symptoms associated with manganese toxicity. The authors called for a reformulation of the multi-trace element products available in the US. The expert who summarized the manganese findings for the 2009 Micronutrient Workshop recommended that manufacturers reformulate multi-trace element products with lower or no manganese, and make single-ingredient trace element products available.[9] This recommendation was formalized in a 2012 ASPEN position statement and again in a 2015 ASPEN call to action.[20,21] The 2012 ASPEN position statement was endorsed by the Society of Critical Care Medicine, American Society of Health-System Pharmacists (ASHP), American Academy of Pediatrics, Academy of Nutrition and Dietetics Dietitians in Nutrition Support Dietetic Practice Group, and the European Society for Clinical Nutrition and Metabolism (endorsed recommended amounts for vitamins, zinc, copper, selenium, and manganese).[22] The ASPEN statements recommended that the manganese dose in parenteral multi-trace element products be decreased to 55 mcg per day for adults, and 1 mcg/kg/day for pediatric and neonatal products with a maximum total dose of 55 mcg per day.[20] The manganese dose for adults (55 mcg per day) was based on a 2002 study by Takagi et al in which 12 patients on long-term home PN received TPN providing 0, 1, 2 or 20 μmol manganese per day.[23] All patients received TPN containing each dose of manganese in sequence over a period of years; the duration of administration at each dose ranged from 6 to 19 months. While no patients showed signs of manganese deficiency or toxicity, manganese concentration in whole blood and magnetic resonance image (MRI) intensity of the globus pallidus increased in a dose-dependent fashion. The MRI findings were considered indicative of manganese accumulation in the brain. Two patients had moderate MRI intensity at 1 μmol (55 mcg) manganese per day, 6 patients had moderate MRI intensity at 2 μmol manganese per day, and 9 patients had moderate MRI intensity at 20 μmol manganese per day. Based on these findings, the authors concluded that "the optimal dose of manganese may be 1 μmol/d for adult patients undergoing home parenteral nutrition."[23] The parenteral multi-trace element products for adults available in the US at the time the 2012 ASPEN position statement was published provided 500-800 mcg of manganese per

day while the pediatric/neonatal products provided 2-10 mcg/kg/day. The pediatric/neonatal parenteral multi-trace element products, Multitrace®-4 Pediatric and Multitrace®-4 Neonatal, are still available in the US today, with the same manganese concentration (25 mcg/ml) as when the ASPEN statement was written in 2012.[20,24,25] The adult parenteral multi-trace element products, Multitrace®-4 and Multitrace®-5, have been discontinued by the manufacturer. A new parenteral multi-trace element formulation from American Regent, Tralement®, was approved by the FDA in July 2020. Tralement® provides manganese sulfate 55 mcg/mL (in combination with zinc, copper and selenium), which aligns with the ASPEN recommendations.[26]

In addition to recommendations to reduce the manganese content in parenteral multi-trace element formulations, the 2009 Micronutrient Workshop and other experts have called for the FDA to require some regulation of trace element contamination in parenteral formulations, or at least labeling requirements that describe the level of trace element contamination, which would allow clinicians to adjust their trace element supplementation accordingly.[9,15] The 2012 ASPEN position statement recommended that manganese contamination be limited to less than 40 mcg per day in adult PN formulations.[20] No recommendation was made for pediatric and neonatal formulations because no contamination data was available for these formulations at that time. Manganese contamination in parenteral products has been shown in several studies, with manganese content of PN formulations without added manganese ranging from 5-38 mcg/L, and up to 310 mcg/L.[9] Magnesium sulfate, calcium gluconate, and potassium chloride contribute to manganese contamination. In his 2009 paper on manganese for the Micronutrient Workshop, Hardy reported the results of his own investigation into manganese contamination of products used to compound home PN, finding manganese levels of 45-90 mcg/L despite reasonable measures to reduce external contamination.[9]

Excess manganese in PN, whether from multi-trace element solutions or contamination, is problematic because manganese is 100% bioavailable with IV administration, and the normal hepatobiliary pathway for manganese elimination is bypassed.[14] Moreover, biliary excretion is often impaired in patients on PN due to cholestasis, particularly in neonates.[9,14] Although a clear relationship between cholestasis and manganese neurotoxicity has not been established, excess manganese has been shown to cause cholestasis in animal models and correlate with severity of cholestasis in infants.[14] In a review on the role of trace elements in PN support of the surgical neonate, Burjonrappa and Miller commented that "Many experts recommend dosing Mn [manganese] in PN solutions on an individual basis rather than as ad hoc trace element combination mixtures."[14] They recommended that manganese supplementation be considered for any infant requiring more than 4 weeks of PN but cautioned that whole blood manganese levels should be monitored in patients on long-term PN, and manganese supplementation discontinued in patients with elevated bilirubin levels.[14] In a 2016 systematic review, the authors concluded that the "widespread" recommendation to provide 55 mcg per day of manganese to patients on long-term home PN was of moderate strength with studies providing mid to high levels of evidence.[27] They found limited evidence to support not providing manganese supplementation, and recommended further investigation to explore the safety of not supplementing manganese in all patients on long-term home PN. The authors recommended that patients with chronic liver disease receive manganese-free PN formulations and suggested that manufacturers "strongly consider producing Mn [manganese]-free multi-trace element solutions."[27]

Neither the FDA Drug Shortages Database nor the ASHP Drug Shortages List included any current or resolved shortages of manganese products.[28,29] In a statement on PN trace element product shortage considerations, the ASPEN Clinical Practice Committee's Nutrition Product Shortage Subcommittee recommended reassessing each patient as to the need for PN and providing enteral nutrition (either oral or assisted) whenever possible, including multi-trace element supplementation if indicated.[30] In

the event of a shortage of IV manganese products, ASPEN stated that there is no need to provide manganese supplementation unless there are clinical signs of deficiency.[30] If clinical signs of manganese deficiency occur, then enteral (oral or assisted) manganese supplementation should be provided if possible.[30]

Table 3. Types of studies

No literature review was conducted

Table 4. Number of studies by country

No literature review was conducted

Table 5. Summary of included studies

No literature review was conducted

Table 6. Dosage by indication – US

No literature review was conducted

Table 7. Dosage by indication – non-US countries

No literature review was conducted

Table 8. Number of studies by combination

	Combination Formula	**Number of Studies**
Nominated	Manganese chloride / Not mentioned – Intravenous solution	0

Table 9. Compounded products – US

No literature review was conducted

Table 10. Compounded products – non-US countries

No literature review was conducted

Results of interviews

One hundred eighty-four SMEs were contacted for interviews; 64 agreed to be interviewed, and 120 declined or failed to respond to the interview request. Thirteen SMEs discussed manganese. Six of these SMEs discussed manganese during interviews conducted in project Year 3; 4 SMEs discussed manganese during interviews conducted in project Year 2; 3 SMEs discussed manganese during interviews conducted in project Years 2 and 3. All 13 SMEs were pharmacists. The SMEs specialized and/or were board-certified in nutrition, working in academic medical institutions, hospitals, an outsourcing facility, and a pharmaceutical company. The SMEs had been in practice for 8 to 43 years.

Manganese chloride was nominated for nutritional supplementation; however, the SMEs had no concerns about manganese deficiency, stating that it is "very rare" and none of them had seen it in their clinical practice. One SME stated, "if a patient is able to eat a diet, I wouldn't worry about manganese." For patients receiving PN, manganese is delivered via multi-trace element solutions added to the PN formulations as well as contamination from other products added to the PN formulation. Several SMEs observed that manganese contaminates components of PN, so patients who receive PN may receive sufficient manganese through contamination alone, without the need for additional manganese from single-ingredient or multi-trace element products. One SME stated "I can't think of any time when we added supplemental manganese for a patient. More often than not, we ended up reducing the dose and their levels were okay, probably from contamination from other sources." One SME cited ASPEN's recommendation for manganese supplementation in PN for a child as 1 mcg/kg/day, but young children "get enough manganese from contamination with other elements, so it does not need to be administered to them." One SME thought that a single-ingredient injectable manganese product was necessary, stating that at their facility, such products were diluted and added separately to PN bags. Other SMEs suggested keeping a single-agent manganese product available might be useful since "having individual trace elements is generally important," and this allows for custom dosing.

Manganese is a trace element that is required for protein synthesis but "not nearly in the dose that was available in the [multi-trace element] formulation" one SME stated, also commenting that the "newer formulations…match the experts' recommendations for manganese dosing"; Tralement®, a multi-trace element injection for use in PN was approved for use in July 2020. One SME remarked that manganese blood levels had not routinely been monitored when the older multi-trace element products were used; this SME thought that manganese levels should be studied with use of the new product (Tralement®), given the drastic reduction in manganese in this product. With the recent availability of Tralement®, this SME did not think that there was enough information to determine whether a single-ingredient injectable manganese product was necessary. One SME mentioned that American Regent, the manufacturer of Tralement®, was planning to re-formulate their multi-trace element product for pediatric patients to align with ASPEN recommended amounts for these patients (information provided on American Regent website confirmed that a new trace element formulation for patients less than 10 kg would be launched in early fall 2021).[31]

Several SMEs expressed concerns about the higher concentrations of manganese nominated for use in combination with other trace elements. One SME stated that they were concerned with the request for higher concentration products because manganese is toxic at low doses; this SME did not "see any value" in products with higher concentrations of manganese. Another SME did not understand the need for products with higher concentrations of manganese, noting that they had never needed to use manganese as an individual product and "first of all, why they're even using it or why they need it. And second, yeah. I'd be a little concerned why you would need such a high dose or concentration. The fluid restriction is the only thing that comes to mind, but it's little bit of a safety concern if there was a mix up." This SME

observed that products with higher concentrations of manganese would not significantly reduce the total amount fluid provided in PN, and in the neonatal population, where excess fluid administration is a particular concern, manganese supplementation is often not necessary: "So maybe in the neonatal population [higher concentration products may be necessary to reduce the amount of fluid administered], but even then I can't think of a reason you would supplement [manganese], especially in premature in neonates, if anything, when their metabolic functions are immature, I'd be a little more worried about the accumulation potentially." When asked about the potential use of manganese in combination with other vitamins and minerals for administration as a cocktail at nutrition centers, this SME commented "It's scary, but in that case, I can't think of why you'd be giving manganese, especially at doses like that… that has a whole different level of safety concerns with giving something faster through a syringe like that."

Most of the SMEs were more concerned with manganese toxicity than manganese deficiency, with one SME commenting that a single-ingredient injectable manganese product "would be more harm than good". Manganese toxicity is especially concerning for patients on long-term PN, since manganese can accumulate over years. According to one SME, "we have been nervous about manganese for many years." The SMEs said that they commonly focus on reducing or removing manganese from PN, with one stating that "individuals on long-term parenteral nutrition usually have elevated manganese levels." One SME pointed out that the recommended manganese dose for adults is 55 mcg per day while, until recently, most multi-trace element solutions provided about 500 mcg a day, "a 10-fold overdose." An SME commented that some institutions stopped using Neotrace-4® (zinc/copper/manganese/chromium), a multi-trace element product, because of the higher manganese concentration; "it's just 5x or 10x more than it should be." Excess manganese can be deposited in the brain, causing neurotoxicity that may manifest as Parkinson's disease-like symptoms. Manganese is eliminated through the biliary tract; patients on PN may not be able to eliminate manganese if their biliary tract is not functioning. Several SMEs had patients who had developed neuropsychological symptoms after receiving PN for 3 to 6 months. One SME said, "all of us have had patients where they have psychosis in the ICU [intensive care unit] and it's like, well, let's take the trace elements out of the formulation, and then in seven days they're much better." Practitioners may not connect neuropsychological symptoms to manganese toxicity. One SME described a young adult patient on a PN mixture formulated with a multi-trace element product who developed Parkinson's-like symptoms over several years, noting that it "took years for the symptoms to start showing up, but [we] were not looking for them." An MRI of this patient showed evidence of manganese accumulation in the brain, and the healthcare team worked with a toxicologist to provide chelation therapy. Another SME noted that 5 to 6 patients had high manganese levels after receiving PN made by a home infusion company that was formulated with a multi-trace element solution; one of these patients was exhibiting neuropsychological signs.

One SME noted that excess manganese is particularly concerning in pediatric patients. A SME who worked in pediatrics said they have between 35 to 40 neonatal intensive care patients and 5 to 10 pediatric intensive care patients on PN a day. This SME used a set PN formulation, but "it is not quite what we want it to be." The SME noted additional challenges, including that single-entity trace elements are not always available, and recent reformulations have led to a price increase. They did not put manganese in any neonatal PN formulation, saying "they really just don't need it" and that in the available products, "it's way too high for them."

Several SMEs had ways of mitigating the risk of excess manganese in PN. One SME stated that since manganese cannot be removed from a multi-trace element product, if there are concerns about manganese toxicity in a patient, then the multi-trace element product is discontinued and each of the required elements (copper, selenium, zinc) is added individually to the PN mixture. Another SME remarked that some facilities will administer manganese as a single-ingredient product only on certain days, in an effort

to reduce the amount of manganese that patients on long-term PN receive. Patients are monitored either by manganese serum levels or symptoms. While the typical practice is to monitor trace element blood levels annually in patients on PN, SMEs noted that more frequent monitoring is needed since patients can "develop a toxicity if they are on [PN mixture formulated with multi-trace element product] longer than 3 months." One SME noted that by monitoring serum levels they see a reduction in manganese levels over time once manganese is removed, although "we don't really know how well that's a marker for true body stores" and they worried about continued neurotoxicity.

A few SMEs had concerns about the effect of different manganese chloride formulations on the stability of PN mixtures. One SME stated that "stability data is necessary in order to utilize a product certainly" but that such data is not always available, particularly when custom products are used in the PN formulation. This SME observed that "there is also a lot of poetic license that gets used or pharmaceutical license from using that information as best you can to interpret whether or not it's a safe formula to provide the patient." Two SMEs indicated that stability is a particular concern for patients who receive PN at home because the PN bags may be stored in the refrigerator for up to 9 days. Stability data, when available, is often only for 24 hours, therefore a lot of information is extrapolated even for existing products and practices. Another SME questioned the use of the chloride salt of manganese, stating "chloride would be an awkward salt for us just because neonates need more acetate and so, to put more chloride in it would be less than ideal."

While trace element shortages are a challenge, most SMEs stated that manganese is the only trace element that has never been in shortage in the past decade; if they wanted to use a single-agent manganese product, they could acquire it. Two SMEs used single-agent manganese products during multi-trace shortages, including manganese chloride and manganese sulfate. In that case, they adjusted dosages based on the ASPEN recommended manganese doses (for parenteral multi-trace element products, 55 mcg per day for adults, and for pediatric and neonatal products 1 mcg/kg/day with a maximum total dose of 55 mcg per day).[20]

Overall, few SMEs acknowledged a need for a single-agent injectable manganese product. Several SMEs saw no need for a single-agent product because manganese is part of multi-trace element products and a contaminant of other trace element solutions, and they do not regularly supplement manganese separately. In addition, several SMEs preferred to administer multi-trace element products rather than single-agent products for safety and ease of use. While single-agent products may address the specific needs of an individual patient, SMEs stated that multi-trace element solutions are more cost-effective and easier to monitor. In addition, multi-trace element solutions are the default choice when zinc, selenium, or copper are on shortage. Availability of the trace elements, as well as difficulties with measuring out the small amounts needed, make it difficult for practitioners to administer them as single agents.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. Forty-three participants attended the event, refer to Table 15 for characteristics of the facilities that the participants represented. A prequestionnaire was also distributed to participants, refer to Tables 15-18 for results of the prequestionnaire.

While a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtain varied from less than 1% to the majority of compounded products used at one participant's facility. A participant stated "we have this method that we use where if we can buy it commercially ready to administer, we do that. If we can't buy it in that format, then we buy it in a vial, for example, that can be snapped into a Mini-Bag Plus, because we're a Baxter house, as a second preference. If we can't buy it in either of those two formats and we can get it from a 503B, then we do that. And our last resort is compounding internally." Two participants commented that they will not outsource a

product unless 2 outsourcing facilities that they contract with are able to compound the product. This redundancy will allow for a quick flip to the other outsourcing facility if there is an issue with a product compounded from one outsourcing facility, minimizing the impact to the participant's facility.

Participants were asked to discuss the decision-making process used at their facility to determine what products to obtain from an outsourcing facility. One major theme that emerged from this discussion was that many of the products purchased from outsourcing facilities are used in critical care areas, like emergency departments and operating rooms. Participants commented that outsourcing facilities are able to provide ready-to-use products that have longer beyond-use-dates compared to products compounded in-house allowing these products to be stocked in automated dispensing cabinets in these units. One participant commented that "we're always going to outsource a PCA [patient controlled analgesia] syringe because we can store it in a Pyxis machine versus us making it and storing it in a fridge." Another participant commented on the benefits of storing medications in an automated dispensing cabinet, stating that "operationally, if you have a STAT medication or something that needs to be delivered within 10 to 15 minutes, if you're looking at us doing it, you're looking at a five-minute gown and glove. If we don't have somebody in the IV [intravenous] room, if you're doing 797 right, it's five minutes. It's four minutes to tube it. It's three minutes to make it, and then you have a dosage system or a camera system, a few minutes more. We are not able to meet that need or they're just contaminating the IV room if they are trying to do it."

Having ready-to-use products available also minimizes the need for compounding and product manipulations to occur on the floor. This can be especially beneficial in children's hospitals as they face a unique need in that they are already having to perform a lot of manipulations to products due to a lack of concentrations or sizes available. One participant commented that "at baseline, already, we manipulate about 80% of what we dispense to patients" and another stated that "there's a number of drugs that require additional manipulation, to get them to a concentration that's appropriate for kids." One participant stated that "we're trying to minimize compounding, expedite actual therapies to patients in that setting [operating room], minimize manipulations as much as possible." Similarly in the emergency department, one participant stated they prefer ready-to-use products for some floor-stock items, like vasopressor infusions, to prevent compounding from occurring on the floor and another commented that "we absolutely buy as many presser drips as we can." One participant remarked that they have received requests from anesthesiologists for products that are commercially available in vials that require manipulation prior to administration to be purchased as syringes from outsourcing facilities stating that "they would prefer to have a syringe form."

Another theme regarding deciding what products to purchase from an outsourcing facility was focused on the utilization and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, like the emergency department and operating room, typically have a high product utilization and overall turnover leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency in which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented that "we look at the impact that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we're going to look to potentially move out." Another participant, while they do not obtain a lot of products from outsourcing facilities, stated that "when we do purchase from 503B's, typically it would be if we just don't have the capacity to keep up with what the demand is." One participant also commented that they will obtain labor intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The COVID-19 pandemic has also impacted the operations of

hospitals with one participant who stated that "it's just really high volume, and the bigger the hospital, the higher the volume, especially when you have one disease state in half of your hospital" and another who expressed that "without 503B, we would've been in significant trouble." One participant commented that "even though the number might be small [percent of products obtained from outsourcing facilities], some of the reasoning is quite critical, and the amount of time that it saves is very significant for beyond what we're able to do and when." Additionally, challenges with recruiting and retaining pharmacy technicians impact decision-making with one participant stating "it is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready to use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing."

In addition to the evaluation of the workload on pharmacy staff, the type and capabilities of the facility also impacted the decision-making process. One participant commented that they do not have an established clean room and therefore perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use-date that can be assigned to these products and, as the participant stated, "we obviously need to provide product with much extensive beyond use dating than we can provide." Several participants also commented that they do not perform high-risk compounding in-house and therefore, all of these products are outsourced. There are challenges with mid-size hospitals being able "to operationalize testing compounds we make for extended stability." One participant stated, "we might make our own syringes if we could get extended dating, but I believe my operations colleagues don't always know how to do this and adhere to the letter of the law."

One participant also commented on the impact that The Joint Commission has had on pushing pharmacies to obtain products from outsourcing facilities. The 2018 medication management standard MM.05.01.07 was intended to move IV admixture preparation out of the nursing unit. This forced pharmacies to consider strategies to make IV admixtures available for use on the floor. Additionally, NPSG.03.04.01 states that all medications and solutions should be adequately labeled, including in operating room and other settings in which procedures are performed. USP <795> and <797> are applicable in operating room settings, stating that products should be labeled and used with one-hour, which may be problematic if syringes are drawn up at the beginning of the day and cases are canceled or delayed. The participant also commented on the cost related to purchasing premade products from manufacturers stating that "predatory pricing on premixes is present in the market."

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products utilized. However, the products utilized in a facility are often developed in-house over decades based on physician and nurse requests, and more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, "these practices had evolved somewhat disparately, even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines." This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said "I think we made nine different epidural concentrations, all driven by anesthesia, and they want what they want and 503Bs may not offer that. No one else in the country is buying that same concentration a 503B isn't going to go through the expense of adding that to their product list." The participant continued that "similar with the ADCs [automated dispensing cabinets], we've run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, 'no, we can't have it, and that's too big it won't fit,' we want it in this format and then we're stuck again because there's

no 503B offering a format during that shortage that fits where it needs to go. Then we're stuck in sourcing." Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that "3% saline for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We're either going to draw that out or we're sending it to the ER with stickers all over it saying only give 150 [mL]." The participant continued that "it would be great if the FDA could look at the size of the container that they're approving and whether that's a realistic dose, is it a unit dose or isn't it."

Participants had differing opinions on the use of outsourcing facilities to obtain drugs during a shortage. Several participants stated that they will typically first restrict use of a drug on shortage, in order to conserve supply, before turning to an outsourcing facility. One participant commented that "most of the time, I will probably pursue restricting, conserving, and looking at all available options prior to going to an outsourcer on my end" and another stated, "I can only think of one time in recent history where we went to an outsourcer." One participant commented that "503Bs can't accept the additional volume if it's a true shortage. If you're not with them pre-shortage, you're not going to get products when you need it during the shortage" continuing that "typically in a shortage, you learn to live without them. You have to." Additionally, in the event of the shortage being the result of lack of an API, outsourcing facilities are likely to be equally affected and unable to provide assistance. However, one participant stated that they first began working with outsourcing facilities because of shortages. This participant commented that "what the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on API. If sterile becomes short, they quickly switch to producing through API, which ASHP [American Society of Hospital Pharmacists] and the FDA allows." This "adds a lot of flexibility so they can bounce back and forth and really try to insulate us from shortages."

A few participants commented on the use of API by outsourcing facilities. One commented that as long as they are conducting end product sterility and stability testing and the product meets quality standards, they are not concerned with the starting ingredients. As long as buyers are familiar with regulations and know what to look for, another participant commented, there should not be any issues with purchasing products compounded starting from API. Another participant stated that as more outsourcing facilities began using API, they became more comfortable with them doing so. However, one participant observed that most outsourcing facilities are switching to sterile-to-sterile and only using API if there is a shortage, stating, "I think the FDA has really looked closely at API, and they're slowly pushing the 503B outsourcers to a sterile to sterile." Only 1 participant commented that they prefer sterile-to-sterile. Another participant stated that the companies they use are all sterile-to-sterile.

A few participants commented on the need for preservative free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative containing product. So, there is a need for this product to be compounded from API as a preservative free product. One participant stated that "if there's not a preservative-free containing option, it really should be something that should be able to be compounded for bulk... especially for the pediatric patient population." However, another participant from a children's hospital stated that the need for a preservative free option has never been a reason why they have obtained a product from an outsourcing facility. Preservative free is also an issue for ophthalmic products, however, one participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing facilities but are not able to, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products but when they reviewed the facilities, they did not pass their internal quality standards; one facility had been banned from distributing products in California by the Board of Pharmacy. There is an

additional challenge with obtaining cephalosporins and beta-lactams due to the potential cross reactivity in patients with allergies. One participant stated that there are some cephalosporins they would like to obtain from an outsourcing facility but cannot because "they would have to build a separate clean room with a dedicated HVAC [heating, ventilation, and air conditioning], so you're talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn't there." Another participant stated that the concentrations required for ophthalmic antibiotics are not available but the labor and risk of compounding these products in-house is not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. LET (lidocaine-epinephrine-tetracaine) gel, for use as a topical anesthetic, was the most commonly obtained product along with buffered lidocaine to put in J-tips. Another participant stated that they obtain diclofenac suppositories from an outsourcing facility due to the high cost of indomethacin suppositories. One participant commented that most of the products they outsource are nonsterile products, generally for oral or topical administration due to a lack of commercially available products being available. The participant stated that they purchase low dose naltrexone for oral use in patients with refractory fibromyalgia and ketamine troches for patients with chronic pain. The participant continued that while the evidence does not support many of the ingredients used in topical pain products, "However, there are select patients. It's very rare that taking that cream away from them actually causes more harm than good." A few participants commented that there is a gap in the market for nonsterile products with one stating "I think that there is a large opportunity for more nonsterile products to be produced by 503Bs." Another stated that as their facility grows and acquires more outpatient clinics, they receive a lot of questions regarding obtaining products for office use. The participant noted that they often have to refer these clinics to outsourcing facilities but stated "there's not many 503Bs are doing the non-sterile for clinic use." As a result, the inpatient pharmacy is often asked to take on this role but "you don't have the space or the staff to do that."

Based on the responses to the prequestionnaire (refer to *Results of survey*), participants were asked questions regarding specific products obtained from outsourcing facilities. Several participants reported using alum (aluminum potassium) as a bladder irrigation for hemorrhagic cystitis refractory to other treatment options. Participants commented that this is high-risk compounding; they purchase alum from an outsourcing facility because they do not perform high-risk compounding in their facility. One participant commented that their policy states that high-risk compounding is not allowed except for alum. This participant wanted to move away from compounding alum in-house and stated that the addition of aluminum potassium to the bulks list might allow this to happen. Another participant had compounded alum in-house from non-sterile ingredients; however, there had been challenges with crystallization after storage. A few participants commented that there is a sterile alum powder available, which they purchase to compound in house. One participant had concerns regarding this powder, stating that "I've talked to that company, but I've had some concerns for them because they don't sell it as a drug. The owner was selling you a chemical, we're selling you a bulk API. It's just sterile. They were fuzzy and I never followed up but, when I asked about their process for verifying the sterility, as you would with a sterile product, we do USP [United States Pharmacopeia] <71> Sterility Testing. They couldn't really give me an answer. They just say they tested for sterility." The participants commented that alum is only needed a few times a year. However, as one participant observed, "when you need it, it's an emergency" and another noting that it "is a challenge for anybody who has the cyclophosphamide-induced hemorrhagic cystitis." As a result, one participant maintains a small inventory of alum product that is purchased from an outsourcing facility but "more times than not, they go unused and expire." Another stated that they do not keep it in stock because there is a minimum purchase and there are only a few cases a year for whom they need to use alum. The participant had it STAT shipped when needed.

Another participant stated that “we had a meeting with the head of urology who was baffled, why they're even ordering it. He was like, ‘this is an old, really old. I don't even know why we're using it’ and basically approved for us to not even make it anymore for now.”

Two participants commented on the use of glycerin at their facility. One stated that they purchase it from a 503A because they were not able to find an outsourcing facility that provides this product. The participant commented that glycerin is used in 3 different concentrations at their facility, 1 for ophthalmic use, 1 for neurologic use in trigeminal neuralgia, and 1 for instilling into “a very specific kind of pump that's used to deliver a very specific kind of chemotherapy.” When there are breaks in the chemotherapy regimen, the pump has to be filled with something and by using glycerin “it can go three months or something like that, so it's a huge patient satisfier to have that concentration available.” The participant also commented that since they have been unable to find an outsourcing facility that compounds the concentration needed for trigeminal neuralgia, they have patients who have been waiting years for treatment. The other participant stated that they compound it in-house but said that it is not done very frequently. The participant commented that it is very difficult to sterilize due to the thickness of the product.

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution in patients undergoing dialysis with one commenting that “our nephrologists, like it in place of heparin for some patients to keep the ports patent or so they don't have to go to alteplase or some of the other drugs.” There is a commercially available product; however, it is only available as a 500 mL bag and the dose needed is typically less than 30 mL. If the syringes are prepared in-house, then the beyond-use-date is limited to 12-24 hours depending on storage which results in waste.

One participant stated that they obtain papaverine from outsourcing facilities for use in urology as Bimix (papaverine/phentolamine) and Trimix (papaverine/phentolamine/alprostadil).

While none of the participants obtained sodium phosphate or aspartic acid from outsourcing facilities for use in cardioplegic solutions, a few commented that they do obtain cardioplegic solutions from outsourcing facilities. The del Nido formulation was the product most commonly obtained. One participant commented that they compound this formulation in-house because the outsourcing facilities did not offer the volume needed at their institution. Another participant commented that while they do obtain the del Nido formulation from an outsourcing facility they also compound a proprietary formulation in house. This participant observed that “it is complicated to do in-house. We do it on a, Baxa 1200 or 2,400, either one, compounder. Then we send it up to for pH and potassium testing. Obviously, then we're confined to 797 beyond-use-dates versus longer beyond-use-dates that we get from the 503B.” Another participant commented that cardioplegic solutions are managed by the perfusion department, not pharmacy, and they use del Nido solution as well as 3 other formulations.

The participants also discussed challenges with utilizing outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because “it just hasn't been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to... It just isn't worth the dating that they gave us or can give us.” Another commented that they obtain very little product from outsourcing facilities due to the “the amount of work for vetting and continually validating quality of these 503B outsourcing facilities.” The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that “Traditionally, we've found 503B's to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed, but we've had some

other smaller 503B's where we've had agreements for certain products to take it off our plate, and then low and behold they're shut down, or closed, or whatever it may be." Minimum purchase amounts were also reported as a concern with one participant stating that "what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients." Another challenge was related to outsourcing facilities utilizing API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration (DEA) places on the quantity that can be produced. The participant stated that "they [outsourcing facilities] want to buy the product that we're trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don't end up with a shortage year after year, after year and then chasing our tail. Also, we may actually want to tell 503Bs, they can't buy those products or that they're limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products, because it actually induces the shortage in many ways."

Results of survey

Zero people responded to the survey distributed via professional medical associations and available on the project website.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 2.2 for survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 15 for respondent characteristics. Amongst respondents, 35 (81% of 43 total respondents) utilized outsourcing facilities to obtain drug products, 4 (9%) did not utilize outsourcing facilities, and 4 (9%) did not respond to this question.

Twenty-seven respondents (19% of 143 responses, where respondents were allowed to select multiple reasons) obtained drug products from outsourcing facilities due to a need for ready-to-use products and 20 respondents (14%) obtained drug products from outsourcing facilities due to backorders (refer to Table 16).

Fourteen respondents (31% of 45 total responses, where respondents were allowed to select multiple types) obtained nonsterile products from outsourcing facilities and 31 (69%) obtained sterile products from outsourcing facilities. Refer to Table 17 for the categories of products obtained from outsourcing facilities.

Zero respondents (0% of 108 responses, where respondents were allowed to select multiple drug products) obtained manganese chloride from a 503B outsourcing facility (refer to Table 18).

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which manganese chloride prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded manganese chloride

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded manganese chloride

No respondents to survey distributed via professional medical associations

Table 15. Demographics of prequestionnaire respondents' facilities

Type of Facility	**Responses, n (N=102)[a]**
Academic medical center	15
Acute care hospital	16
Children's hospital	8
Community hospital	11
Critical access hospital	2
Dialysis center	2
Federal government hospital	4
Health system	15
Inpatient rehabilitation center	4
Long-term acute care hospital	3
Outpatient surgery center	6
Rural hospital	2
Skilled nursing facility	0
Specialty hospital[b]	4
Trauma center	5
Urban hospital	5
Number of Beds	**Responses, n (N=38)**
< 50	4
50-99	3
100-199	1

200-299	3
300-399	5
400-599	3
> 600	18

[a]Respondents allowed to select more than one type of facility.
[b]Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, oncology.

Table 16. Reasons for obtaining products from outsourcing facilities

Categories	**Responses, n (N=143)[a]**
Backorders	20
Convenience	19
Cost	10
Need for concentrations not commercially available	19
Need for multi-ingredient products not commercially available	10
Need for preservative-free products	3
Need for ready-to-use products	27
No FDA-approved product available	7
No onsite compounding facility	1
Onsite compounding facility not equipped to compound all necessary products	19
Other[b]	6

[a]Survey respondents allowed to select multiple categories.
[b]Survey respondents reported staffing shortages, need for extended dating, volume of product used, standardization projects as additional reasons for utilizing outsourcing facilities.

Table 17. Categories of products obtained from outsourcing facilities

Categories	**Responses, n (N=142)[a]**
Cardioplegic solutions	14
Dermatologic preparations	6

Dialysate solutions	0
Fluids	8
Ophthalmic preparations	10
Patient-controlled analgesia	20
Ready-to-use anesthesia syringes	25
Ready-to-use antibiotic syringes and/or bags	14
Ready-to-use electrolyte solutions	5
Ready-to-use vasopressor solutions	18
Total parenteral nutrition solutions	16
Other[b]	6

[a]Survey respondents allowed to select multiple categories.
[b]Survey respondents reported obtaining alum for bladder irrigation, oxytocin, anticoagulant sodium citrate solution, narcotic drips, high-cost anti-seizure medications, antiviral medications, topical pain, oral tablets/capsules.

Table 18. Products obtained from an outsourcing facility

Procedure Type	**Responses, n (N=108)[a]**
Acetylcysteine	1
Adenosine	2
Aluminum potassium sulfate	2
Aspartic acid	0
Atenolol	0
Atropine	9
Baclofen	4
Betamethasone	0
Biotin	0
Bupivacaine	8
Calcium chloride	1
Caffeine sodium benzoate	0

Cholecalciferol	1
Chromium chloride	0
Clonidine	0
Dexamethasone sodium phosphate	0
Diclofenac	0
Gentamicin	0
Glycerin	1
Hydroxyzine	0
Ketamine	14
Levocarnitine	0
Lidocaine	8
Lorazepam	2
Magnesium sulfate	4
Manganese chloride	0
Methylprednisolone	0
Midazolam	15
Mupirocin	1
Norepinephrine	15
Ondansetron	0
Phytonadione	0
Potassium chloride	0
Potassium phosphate	0
Prilocaine	0
Proline	0
Propranolol	1
Ropivacaine	6

Sodium chloride	0
Sodium citrate	3
Sodium phosphate	0
Tetracaine	2
Triamcinolone acetonide	0
Tropicamide	0
None of the above	8

[a]Survey respondents were allowed to select multiple products.

CONCLUSION

Manganese chloride was nominated for inclusion on the 503B Bulks List as an IV injection for nutritional supplementation. Manganese chloride was nominated for use in combination with other trace elements. Manganese chloride is available as an FDA-approved injectable solution. Manganese sulfate is available in combination with cupric sulfate, selenious acid and zinc sulfate as an FDA-approved IV solution (Tralement®). Manganese chloride is available in the nominated dosage form and ROA in Australia, Belgium, Canada, Hong Kong, Ireland, and Latvia.

No literature review was conducted; however, several studies were identified that provided valuable information about the use of parenteral manganese. The recommended parenteral daily dose of manganese has changed over time from 1979 and 1984 when the NAG-AMA and AMA and The New York Academy of Medicine recommended 150-800 mcg and 400-800 mcg, respectively to 1998 and 2004 when ASPEN recommended 60-100 mcg to the present recommendation for 55 mcg per day for adults and 1 mcg/kg/day for pediatrics and neonates. The decrease in dose recommendations was prompted by reports of neurotoxicity in children due to excess manganese and studies that showed high manganese in the blood and tissues of patients receiving long-term PN. There has been only one report of manganese deficiency in a clinical setting. Concern for manganese toxicity in patients receiving PN has also prompted ASPEN and individual experts to call for a reduction or elimination of manganese in multi-trace element products and labels that provide the level of trace element contamination in PN formulations. The first FDA-approved multi-trace element product with the ASPEN recommended parenteral daily dose of manganese for adults (55 mcg per day) was introduced in 2020.

All of the SMEs who specialized in nutrition were more concerned with manganese toxicity with PN than manganese deficiency, particularly in pediatric patients or those who receive PN for a prolonged duration. SMEs typically added manganese to PN mixtures via multi-trace element solutions, which are safer, easier to use and more cost effective than adding trace elements as single-ingredient products. Several SMEs mentioned that a recently approved multi-trace element product, Tralement®, has a lower concentration of manganese that aligns with ASPEN recommendations for manganese supplementation in PN. A pediatric version of this product is forthcoming. A few SMEs thought that the availability of single-ingredient injectable manganese products was important because these products allow for customized dosing. However, the effect of different manganese chloride formulations on the stability of PN mixtures is unknown. Several SMEs expressed concerns about the higher concentrations of manganese nominated for use in combination with other trace elements. Most SMEs stated that manganese is the only trace element that has never been in shortage in the past decade.

There were no respondents to the survey distributed via professional medical associations. From the prequestionnaire, 0 respondents reported obtaining manganese chloride from an outsourcing facility.

REFERENCES

1. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. *International Journal of Social Research Methodology: Theory and Practice.* 2005;8(1):19-32.
2. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol.* 2014;67(12):1291-1294.
3. Levac D, Colquhoun H, O'Brien KK. Scoping studies: Advancing the methodology. *Implementation Science.* 2010;5(1).
4. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *International Journal of Evidence-Based Healthcare.* 2015;13(3):141-146.
5. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol.* 2018;18(1):143-143.
6. Evans GR, Masullo LN. Manganese toxicity. In: *StatPearls.* Treasure Island (FL): StatPearls Publishing; 2020.
7. Hardy G, Menendez AM, Manzanares W. Trace element supplementation in parenteral nutrition: Pharmacy, posology, and monitoring guidance. *Nutrition.* 2009;25(11-12):1073-1084.
8. Williams-Johnson M. *Manganese and its compounds.* Geneva, Switzerland: World Health Organization;1999.
9. Hardy G. Manganese in parenteral nutrition: who, when, and why should we supplement? *Gastroenterology.* 2009;137(5 Suppl):S29-35.
10. Manganese. National Institutes of Health Office of Dietary Supplements. https://ods.od.nih.gov/factsheets/Manganese-HealthProfessional/#en1. Published 2019. Updated February 14, 2020. Accessed May 12, 2020.
11. Aschner M, Erikson K. Manganese. *Adv Nutr.* 2017;8(3):520-521.
12. Norose N, Terai M, Norose K. Manganese deficiency in a child with very short bowel syndrome receiving long-term parenteral nutrition. *J Trace Elem Exp Med.* 1992;5:100-101.
13. Hardy IJ, Gillanders L, Hardy G. Is manganese an essential supplement for parenteral nutrition? *Curr Opin Clin Nutr Metab Care.* 2008;11(3):289-296.
14. Burjonrappa SCM, M. Role of trace elements in parenteral nutrition support of the surgical neonate. *J Pediatr Surg.* 2012;47(4):760-771.
15. Buchman AL, Howard LJ, Guenter P, Nishikawa RA, Compher CW, Tappenden KA. Micronutrients in parenteral nutrition: Too little or too much? The past, present, and recommendations for the future. *Gastroenterology.* 2009;137(5 SUPPL):S1-S6.
16. Shils ME, White PL. Introduction to trace element conference. *Bull N Y Acad Med.* 1984;60(2):115-117.
17. Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. *JPEN Journal of parenteral and enteral nutrition.* 2004;28(6):S39-S70.
18. National Advisory Group On Standards And Practice Guidelines For Parenteral Nutrition. Safe practices for parenteral nutrition formulations. *JPEN J Parenter Enteral Nutr.* 1998;22(2):49-66.

19. Howard L, Ashley C, Lyon D, Shenkin A. Autopsy tissue trace elements in 8 long-term parenteral nutrition patients who received the current u.S. Food and drug administration formulation. *JPEN J Parenter Enteral Nutr.* 2007;31(5):388-396.

20. 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.

21. 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.

22. Vanek VW. Review of trace mineral requirements for preterm infants: What are the current recommendations for clinical practice? *Nutr Clin Pract.* 2015;30(5):720-721.

23. Takagi Y, Okada A, Sando K, Wasa M, Yoshida H, Hirabuki N. Evaluation of indexes of in vivo manganese status and the optimal intravenous dose for adult patients undergoing home parenteral nutrition. *Am J Clin Nutr.* 2002;75(1):112-118.

24. *Multitrace-4 Neonatal [package insert].* Shirley, NY: American Regent, Inc.; August 2018.

25. *Multitrace-4 Pediatric [package insert].* Shirley, NY: American Regent, Inc.; August 2018.

26. *Tralement [package insert].* Shirley, NY: American Regent, Inc.; July 2020.

27. Baker BA, A. Isenring, L. Recommendations for manganese supplementation to adult patients receiving long-term home parenteral nutrition: An analysis of the supporting evidence. *Nutr Clin Pract.* 2016;31(2):180-185.

28. Food and Drug Administration. Drug Shortages. U.S. Food and Drug Administration (FDA). https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages. Updated January 29, 2021. Accessed March 26, 2021.

29. University of Utah Drug Information Service. Current Drug Shortages. American Society of Health-System Pharmacists (ASHP). https://www.ashp.org/Drug-Shortages/Current-Shortages. Accessed March 26, 2021.

30. Plogsted S, Adams SC, Allen K, et al. Parenteral nutrition trace element product shortage considerations. American Society for Parenteral and Enteral Nutrition (ASPEN). https://www.nutritioncare.org/News/General_News/Parenteral_Nutrition_Trace_Element_Product_Shortage_Considerations/. Published 2016. Updated July 20, 2016. Accessed February 25, 2021.

31. Multitrace-4. American Regent, Inc. https://www.americanregent.com/our-products/multitrace-4/. Published 2021. Accessed June 6, 2021.

APPENDICES

Appendix 1. Search strategies for bibliographic databases

No literature review was conducted.

Appendix 2.1. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer manganese chloride to your patients?
    - Yes
    - No
3. Do you prescribe or administer manganese chloride by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Intravenous solution
    - None of the above
4. I prescribe or administer manganese chloride for the following conditions or diseases: (check all that apply)
    - Manganese supplementation in parenteral nutrition
    - Other (please explain) _____
5. I prescribe or administer manganese chloride in combination with other active pharmaceutical ingredients as a multi-ingredient product.
    - Yes
    - No
6. I prescribe or administer manganese chloride to my patients as the following: (check all that apply)
    - FDA-approved drug product
    - Compounded drug product
    - Other (please explain) _____
7. I use compounded manganese chloride because: (check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
    - Patient allergies prevent me from using commercially available products (please explain) _____
    - Patient conditions prevent me from using commercially available products (please explain) _____
    - I am not aware of any commercially available products containing manganese chloride
    - Other (please explain) _____
8. Do you stock non-patient-specific compounded manganese chloride at your practice?
    - Yes

- No
- I'm not sure

9. I obtain compounded manganese chloride from the following: (check all that apply)
    - Compound myself at my practice
    - Have the product compounded by an in-house pharmacy
    - Purchase, or have a patient purchase, from a compounding pharmacy
    - Purchase, or have a patient purchase, from an outsourcing facility
    - Other (please explain) _____
10. What is your practice setting? (check all that apply)
    - Physician office/private practice
    - Outpatient clinic
    - Hospital/health system
    - Academic medical center
    - Emergency room
    - Operating room
    - Other (please describe) _____
11. What degree do you hold? (check all that apply)
    - Doctor of Medicine (MD)
    - Doctor of Osteopathic Medicine (DO)
    - Doctor of Medicine in Dentistry (DMD/DDS)
    - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - Naturopathic Doctor (ND)
    - Nurse Practitioner (NP)
    - Physician Assistant (PA)
    - Other (please describe) _____

Appendix 2.2. Survey instrument for pharmacy roundtable prequestionnaire

1. Please select all that apply regarding the facility with which you are affiliated.
    - Academic medical center
    - Acute care hospital
    - Children's hospital
    - Community hospital
    - Critical access hospital
    - Dialysis center
    - Federal government hospital
    - Health system
    - Inpatient rehabilitation center
    - Long-term acute care hospital
    - Outpatient surgery center
    - Rural hospital
    - Skilled nursing facility
    - Specialty hospital, please identify specialtiy(ies)
    - Trauma center
    - Urban hospital
2. Please select the number of beds in the facility with which you are affiliated.
    - < 50
    - 50-99
    - 100-199
    - 200-299
    - 300-399
    - 400-599
    - > 600
3. Do you use an outsourcing facility (503b facility) to obtain any products used in your facility? A list of FDA registered outsourcing facilities can be found at https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilites.
    - Yes
    - No
4. Why do you use an outsourcing facility to obtain product(s)? Please select all that apply
    - Backorders
    - Convenience
    - Cost
    - Need for concentrations not commercially available
    - Need for preservative-free products
    - Need for ready-to-use products
    - No FDA-approved products available
    - No onsite compounding facility
    - Onsite compounding facility not equipped to compound all necessary products
    - Other, please explain _____
5. Please select the type(s) of products obtained from an outsourcing facility.
    - Nonsterile products
    - Sterile products
6. Please select the category(ies) of products obtained from an outsourcing facility.
    - Cardioplegic solutions
    - Dermatologic preparations
    - Dialysate solutions

- Fluids
- Ophthalmic preparations
- Patient-controlled analgesia
- Ready-to-use anesthesia syringes
- Ready-to-use antibiotic syringes and/or bags
- Ready-to-use electrolyte solutions
- Ready-to-use vasopressor solutions
- Total parenteral nutrition solutions
- Other, please identify _____

7. From the list below, please select the drug(s) that you obtain as either a single ingredient or multi-ingredient product from an outsourcing facility.
    - Acetylcysteine
    - Adenosine
    - Aluminum potassium sulfate
    - Aspartic acid
    - Atenolol
    - Atropine
    - Baclofen
    - Betamethasone
    - Biotin
    - Bupivacaine
    - Calcium chloride
    - Caffeine sodium benzoate
    - Cholecalciferol
    - Chromium chloride
    - Clonidine
    - Dexamethasone sodium phosphate
    - Diclofenac
    - Gentamicin
    - Glycerin
    - Hydroxyzine
    - Ketamine
    - Levocarnitine
    - Lidocaine
    - Lorazepam
    - Magnesium sulfate
    - Manganese chloride
    - Methylprednisolone
    - Midazolam
    - Mupirocin
    - Norepinephrine
    - Ondansetron
    - Phytonadione
    - Potassium chloride
    - Potassium phosphate
    - Prilocaine
    - Proline
    - Propranolol
    - Ropivacaine
    - Sodium chloride
    - Sodium citrate

- Sodium phosphate
- Tetracaine
- Triamcinolone acetonide
- Tropicamide
- None of the above

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Anesthesiology	Society of Cardiovascular Anesthesiologists	Declined – failed to respond
Cardiology	American Academy of Cardiovascular Perfusion	Declined
	American Board of Cardiovascular Perfusion	Declined – failed to respond
	American Society of Extracorporeal Technology	Declined – failed to respond
Dermatology	American Academy of Dermatology	Declined – failed to respond
Naturopathy	American Association of Naturopathic Physicians	Agreed
Nephrology	American Society of Diagnostic and Interventional Nephrology	Declined
Ophthalmology	American Academy of Ophthalmology	Declined – failed to respond
	American Society of Cataract and Refractive Surgery	Agreed
	American Society of Retina Specialists	Declined
Podiatry	American Podiatric Medical Association	Agreed
Psychiatry	The International Society for Electroconvulsive Therapy and Neurostimulation	Agreed
Rheumatology	American College of Rheumatology	Agreed
Surgery	American Association of Neurological Surgeons	Declined – failed to respond
	American Association for Thoracic Surgery	Declined – failed to respond
	American College of Surgeons	Declined – failed to respond
	American Society for Reconstructive Microsurgery	Declined – failed to respond
Urology	Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction	Declined
Wound Care	Association for the Advancement of Wound Care	Declined – failed to respond

[a]Associations that declined in Year 1 and/or Year 2 were not contacted in Year 3.