Summary Report

Sodium phosphate, USP

Prepared for:

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

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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.

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Frequently Used Abbreviations

2,3-DPG	2,3-diphosphoglycerate
ATP	Adenosine triphosphate
API	Active Pharmaceutical Ingredient
ASPEN	American Society of Enteral and Parenteral Nutrition
EMA	European Medicines Agency
EU	European Union
FGF-23	Fibroblast growth factor-23
FDA	Food and Drug Administration
IRB	Institutional Review Board
ICU	Intensive care unit
IV	Intravenous
OTC	Over-the-counter
PTH	Parathyroid hormone
PN	Parenteral nutrition
ROA	Route of administration
SME	Subject matter expert
TPN	Total parenteral nutrition
UK	United Kingdom
US	United States
USP	United States Pharmacopeia

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of sodium phosphate, USP (UNII code: SE337SVY37), 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 sodium phosphate 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 sodium phosphate 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 sodium phosphate 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 NOMINATION

Sodium phosphate was nominated for inclusion on the 503B Bulks List by US Compounding Pharmacy. Sodium phosphate was nominated for electrolyte management via an intravenous (IV) solution.

The nominator did not provide references from published peer-reviewed literature to describe the pharmacology and support the clinical use of sodium phosphate.

The reason provided for nomination to the 503B Bulks List was manufacturer backorder.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of sodium phosphate 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 sodium phosphate; name variations of sodium phosphate 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

sodium phosphate USP. 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

Sodium phosphate is a component of an FDA-approved product that is currently available. The nominated product 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 sodium phosphate was used in a clinical setting. The systematic literature review and indication from the nomination were reviewed to identify medical specialties that would potentially use sodium phosphate. 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 sodium phosphate 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

- Sodium phosphate is available as an FDA-approved monobasic and dibasic injectable product.
- Sodium phosphate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for sodium phosphate.
- Sodium phosphate is available in the nominated dosage form and ROA in Abu Dhabi and Saudi Arabia.

Table 1. Currently approved products – US

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Sodium phosphate monobasic anhydrous / Sodium phosphate dibasic heptahydrate	276 mg/mL / 142 mg/mL	Injection	Injectable	Prescription	5/10/1983

[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

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
Sodium phosphate	3 mmol 45 mmol/15 mL	Solution	Intravenous	Abu Dhabi	Active	–
	45 mmol			Saudi Arabia	Prescription	–

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.

Results of literature review

No literature review was conducted.

Pharmacology and historical use

Phosphorus is the predominant intracellular anion in the body.[6] The majority of phosphorus (85%) is located in bone and teeth; the remaining phosphorus is found in soft tissues (14%) and extracellular fluid (1%).[6,7] Besides being an essential structural component of bone and teeth, phosphorus is a component of cell membranes and nucleic acids.[6,8] Phosphorus also plays a critical role in cellular metabolism by storing energy in adenosine triphosphate (ATP), regulating cellular processes via phosphorylation and dephosphorylation, and helping to maintain acid-base homeostasis.[6,8] In addition, phosphorus is involved in the synthesis and functioning of 2,3-diphosphoglycerate (2,3-DPG), which regulates the release of oxygen from hemoglobin in peripheral tissues.[8-10]

Phosphorus homeostasis is a balance between dietary intake and gastrointestinal absorption, bone deposition and resorption, and urinary excretion. Phosphorus is available in a variety of foods, including milk, fish, poultry, meat, eggs and peanuts.[10] Phosphorus is readily absorbed from the gastrointestinal tract and filtered by the kidneys. Under normal conditions, approximately 80% of the phosphorus filtered by the glomeruli is reabsorbed at the proximal convoluted tubule.[6,10] Phosphorus levels are regulated by parathyroid hormone (PTH), 1,25-dihydroxyvitamin D3 (calcitriol) and fibroblast growth factor-23 (FGF-23).[9,10] PTH stimulates bone resorption and subsequent release of calcium and phosphorus, renal excretion of phosphorus and activation of 1,25-dihydroxyvitamin D3. This active form of vitamin D increases calcium and phosphorus absorption from the gastrointestinal tract and has a synergistic effect with PTH on bone.[9,10] FGF-23, which is released from osteoblasts and osteocytes, enhances renal excretion of phosphorus and inhibits the formation of 1,25-dihydroxyvitamin D3, thereby decreasing calcium and phosphorus absorption from the gastrointestinal tract.[9-11]

Normal serum phosphorus levels in adults are 2.5 to 4.5 mg/dL. Neonates, infants and children have higher reference values.[7] Hypophosphatemia is defined as serum phosphorus less than 2.5 mg/dL, with mild hypophosphatemia in the range of 1.8 to 2.5 mg/dL, moderate hypophosphatemia in the range of 1.0 to 1.7 mg/dL and severe hypophosphatemia less than 1.0 mg/dL.[6,7] Hypophosphatemia develops due to decreased phosphorus intake or absorption, increased intracellular uptake and/or increased renal loss. Decreased dietary intake alone rarely leads to hypophosphatemia; more often, decreased phosphorus intake exacerbates hypophosphatemia.[6] Decreased gastrointestinal absorption of phosphorus can occur with conditions that cause malabsorption, vomiting and/or diarrhea.[6,12] Certain medications, such as aluminum-, calcium- and magnesium-containing antacids, phosphate binders and sucralfate, can impair phosphorus absorption.[9] Shift of phosphorus from the extracellular to intracellular space, due to alkalosis, endogenous or exogenous insulin or catecholamines, rapid cell proliferation or hungry bone syndrome, can contribute to or cause hypophosphatemia.[6,9] Beta-adrenergic agonists, such as albuterol, epinephrine, isoproterenol and terbutaline, stimulate the intracellular shift of phosphorus. Theophylline, erythropoietin and colony stimulating factors also promote the shift of phosphorus from the extracellular to intracellular space.[9] Increased renal excretion of phosphorus may occur due to: primary or secondary hyperparathyroidism; vitamin D deficiency; continuous renal replacement therapy; renal transplantation; Fanconi syndrome; or congenital or genetic disorders.[6,9] Several medications, including diuretics, carbonic anhydrase inhibitors, calcitonin and corticosteroids, enhance renal phosphorus loss.[9,11] Alcohol or alcoholism can lead to hypophosphatemia through all the aforementioned mechanisms.[9,11]

Refeeding syndrome is a condition associated with imbalance of several electrolytes, including phosphorus. This condition is "best described as the adverse clinical and biochemical problems that can result from feeding severely malnourished patients via any route, be it oral, enteral or parenteral."[13] During starvation, the body is in a catabolic state, breaking down first glycogen stores and then fat and muscle for energy and amino acids. In order to conserve energy, the body's metabolism decreases, which down-regulates energy-consuming processes.[13] With initiation of oral, enteral or parenteral feeding, the provided carbohydrates (or glucose) stimulate insulin release, which precipitates cellular uptake of glucose, electrolytes (phosphorus, potassium and magnesium) and thiamine.[13,14] This intracellular shift of electrolytes results in hypophosphatemia, the hallmark of refeeding syndrome, hypokalemia and hypomagnesemia. The intracellular shift of thiamine leads to thiamine deficiency, which can exacerbate the electrolyte deficiencies.[13] Insulin also increases sodium reabsorption from the distal nephron, which leads to water retention and potentially fluid overload.[13,14]

Clinical signs of hypophosphatemia vary depending on the degree, duration and underlying cause of low phosphate levels.[7] Acute hypophosphatemia due to transcellular shift alone, even if severe, may not be clinically significant in the absence of phosphate depletion.[12] Acute, severe hypophosphatemia with depletion of phosphate typically results in clinical signs and requires treatment.[12] Many of the clinical signs associated with hypophosphatemia are related to decreased availability of ATP and 2,3-DPG.[13] These signs include neuromuscular weakness, rhabdomyolysis and red blood cell, white blood cell and platelet dysfunction.[7,13] Neuromuscular weakness may manifest as a lower motor neuron-type paralysis, cranial nerve palsies and reduced functioning of the diaphragmatic muscles, leading to respiratory failure.[7,13] Altered mental status, tremors and seizure may also occur with hypophosphatemia. Low phosphorus levels may cause decreased myocardial contractility, arrhythmias and low blood pressure.[6,13] Chronic hypophosphatemia hinders bone mineralization, leading to osteomalacia, bone pain and possibly fractures.[7]

The prevalence of hypophosphatemia in hospitalized patients varies depending on the patient's underlying condition. The prevalence of hypophosphatemia is higher in patients with sepsis, alcoholism, major trauma, diabetic ketoacidosis, renal transplantation and pre-existing malnourishment.[6,7,15] A direct relationship between low phosphorus and mortality has been hard to establish due to the difficulty of eliminating confounding factors.[12] Two recent systematic reviews have explored this relationship. Blaser *et al* attempted to answer multiple questions about the treatment and morbidity of hypophosphatemia.[16] The authors found insufficient evidence to answer their questions, concluding "It is likely that hypophosphatemia affects several organ systems and impairs outcome in critically ill adults and children…the exact cut-off of serum/plasma phosphate level and magnitude of the clinical impact remain unclear: the optimal frequency of measurements, target serum phosphate, and repletion strategy are also uncertain."[16] In another systematic review published in 2020, Sin *et al* focused on the relationship between hypophosphatemia and intensive care unit (ICU) length of stay, hospital length of stay and mortality in ICU patients.[17] Twelve cohort studies with 7626 patients were included. Patients with hypophosphatemia had a higher risk of mortality compared to those who did not; this effect was not statistically significant and there was heterogeneity amongst the studies. Patients with hypophosphatemia did not have a significantly higher risk of in-hospital mortality compared to those without hypophosphatemia. The pooled relative risk of mortality in patients with hypophosphatemia was 1.08 (95% confidence interval 0.86-1.36) after adjusting for confounding factors. ICU length of stay was 2.22 days longer in patients with hypophosphatemia compared to those without, with significant heterogeneity. Hospital length of stay was a mean of 2.19 days longer in patients with hypophosphatemia compared to those without,

with no heterogeneity. Patients with hypophosphatemia had a mean 1.31 days longer on mechanical ventilation compared to those without hypophosphatemia; this increase was nonsignificant and significant heterogeneity was present. The authors concluded that while "Hypophosphatemia appears to be a marker of disease severity…the causative role of hypophosphatemia in mortality remains uncertain."[17]

The goals of therapy in patients with low phosphate are to avoid or resolve symptoms of hypophosphatemia, return serum phosphate concentration to normal range, and prevent hyperphosphatemia or other electrolyte disturbances.[8] Patients with mild to moderate hypophosphatemia are often asymptomatic and therefore, do not require urgent phosphate repletion.[6] Oral phosphate and vitamin D supplementation are recommended for these patients.[7] Oral supplementation is preferable to IV because this ROA reduces the possibility of an abrupt, large increase in serum phosphorus and rebound hyperphosphatemia.[12] However, oral phosphate supplements may cause diarrhea and abdominal pain and their absorption is unpredictable.[7,8,12] The recommended daily dose for oral phosphate supplementation in patients with mild to moderate hypophosphatemia is 1000 mg or 0.3 mmol/kg.[6,14] If a patient with mild to moderate hypophosphatemia cannot tolerate oral or enteral phosphate supplementation, has impaired respiratory function, or is otherwise symptomatic, then IV phosphate may be provided.

IV phosphate administration is recommended for patients with severe hypophosphatemia (less than 1.0 mg/dL). Sodium phosphate is recommended for IV supplementation in most patients, although caution must be exercised in patients who are volume overloaded.[8,12,18] Potassium phosphate is recommended for patients who are also hypokalemic. In patients with mild hypophosphatemia and normal renal function, the IV phosphate replacement dose is 0.08 to 0.2 mmol/kg or 0.3 mmol/kg/day.[8,9,12,14] In patients with moderate hypophosphatemia and normal renal function, the IV phosphate replacement dose is 0.16 to 0.4 mmol/kg or 0.6 mmol/kg/day.[8,9,12,14] In patients with severe hypophosphatemia and normal renal function, the IV phosphate replacement dose is 0.32 to 0.6 mmol/kg or 0.6 mmol/kg/day.[8,9,12,14] Doses for phosphate replacement should be reduced by at least 50% in patients with renal insufficiency.[8,12] Total daily phosphate supplementation should not exceed 50 mmol, although doses up to 1 mmol/kg have been reported in critically ill adult trauma patients.[9,14] The American Society of Parenteral and Enteral Nutrition (ASPEN) recommends a phosphate dose of 20 to 40 mmol/day for adults receiving parenteral nutrition (PN), with adjustments for high dextrose intake and/or refeeding.[19] This is equivalent to approximately 10 to 15 mmol of phosphate per 1000 kilocalories.[9] The ASPEN recommended phosphate dose for preterm neonates and infants or children receiving PN is 1 to 2 mmol/kg/day and 0.5 to 2 mmol/kg/day, respectively.[19] The ASPEN recommended phosphate dose for adolescents and children > 50 kg receiving PN is 10 to 40 mmol/day.[19] The primary safety concerns associated with phosphates injections are rapid IV administration and incompatibility with calcium.[20] To prevent phlebitis and electrolyte derangements, phosphates injections should be thoroughly diluted and mixed prior to administration and infused slowly.[20] The maximum recommended infusion rate for phosphate is 7 to 7.5 mmol per hour, although rates up to 10 to 15 mmol per hour have been reported.[8,9,21] IV sodium or potassium phosphate administration may cause or exacerbate hypernatremia, hyperkalemia, hyperphosphatemia or hypocalcemia.[6,12] Serum electrolytes levels should be checked regularly while a patient is receiving IV sodium or potassium phosphate. IV phosphate administration may lead to the formation of calcium phosphate precipitates, which can deposit throughout the body and lead to acute kidney injury, pulmonary thromboembolism, and other complications.[6,12]

There have been multiple reports in the literature of insoluble calcium phosphate precipitates forming in patients receiving PN, resulting in catheter occlusion, respiratory distress and even death.[22-25] In

1994, the FDA issued a safety alert to call attention to the risk of precipitate formation in PN admixtures.[26] A few years later, in 1996, Hill *et al* described massive pulmonary embolism and subsequent death in two patients who received total PN (TPN) with calcium gluconate and potassium phosphate.[22] On autopsy, the emboli were found to contain an amorphous material consisting of calcium and phosphorus. To understand how these deaths occurred and avoid future complications, the authors administered the TPN mixture that the patients had received to healthy pigs. The pigs died within 4 hours of beginning the PN infusion; in necropsy, material similar to that found in the human patients' lungs was found in the pig's lungs. The authors also evaluated the composition and preparation of the TPN mixture that had been administered to the patients. They found that the pH of the amino acid component, transient elevations in calcium and phosphorus during mixing and lack of sufficient agitation facilitated the formation of the calcium phosphate material. In 1999, Reedy *et al* reported the sudden death of a patient on long-term PN.[24] The patient was diagnosed with pulmonary thromboembolism after computed tomography scan revealed nodular opacities throughout the lungs and biopsy showed material compatible with crystals from calcium phosphate precipitation. The patient recovered but died suddenly at home less than one month after hospital discharge. On autopsy, the patient had precipitates in the lungs similar to those that had been seen in the earlier biopsy specimens.

The critical factors influencing calcium and phosphate compatibility in solution are the pH of the solution and the calcium and phosphate concentrations of the solution.[20] Phosphate exists in 3 anionic forms, all of which can combine with calcium to form insoluble precipitates.[20] The pH of the solution affects which forms predominate; a lower pH favors a higher concentration of $H_2PO_4^-$ (dihydrogen or monobasic phosphate), which forms the more soluble calcium dihydrogen phosphate salt ($Ca[H_2PO_4]_2$). This salt is 60 times more soluble than the calcium monohydrogen phosphate salt ($CaHPO_4$) because $CaHPO_4$ is less dissociated.[27] Inorganic salts, such as calcium chloride, sodium phosphate and potassium phosphate, dissociate more extensively than organic salts, such as calcium gluconate and sodium glycerophosphate, thereby providing more substrate to form calcium phosphate compounds.[20] For this reason, calcium chloride should never be used in IV mixtures that contain phosphates.[27] Currently, there are no FDA-approved single-ingredient sodium glycerophosphate products available in the US. According to Newton and Driscoll (who cited Hicks and Hardy), "The introduction of i.v. organic phosphate salts in the United States would greatly improve the compatibility profile of total parenteral nutrient admixtures that contain calcium supplements."[20]

In addition to the pH, the calcium and phosphate concentrations of a solution affect calcium and phosphate compatibility. When calculating calcium and phosphate concentrations, all possible sources of these electrolytes in the solutions should be accounted for.[27] The product of calcium and phosphate concentrations should not be the sole criteria used to evaluate compatibility because this product varies inconsistently as calcium concentration decreases and phosphate concentration increases.[27] The principal components of the solution, namely dextrose, amino acids and fat, also influence calcium and phosphate compatibility. Dextrose, amino acids, and fat affect the pH of the solution while some amino acids form stable soluble complexes with calcium, thereby removing it from solution.[27]

The 2014 ASPEN clinical guidelines on ordering, order review, compounding, labeling and dispensing PN addressed a series of questions including the most appropriate recommendations for optimizing calcium (gluconate) and sodium or potassium phosphate compatibility in PN admixtures.[28] The evidence available to answer this question was weak and the guideline authors concluded "We cannot make a recommendation due to the multiple variations in amino acid concentrations, PN volume, pH, presence or absence of fat emulsion, and the amounts of other minerals (eg,

magnesium)."[28] The authors suggested that healthcare professionals consult published solubility curves for guidance on the maximum amount of calcium and phosphate that can be added to a solution. The authors cautioned that there is a paucity of evidence to demonstrate the stability of PN solutions beyond 48 hours. The 2014 ASPEN PN safety consensus recommendation advised that healthcare organizations should develop protocols that allow PN orders to be modified if potential incompatibilities are identified; any modifications should be documented and communicated to the healthcare team.[29] When preparing PN solutions, sodium or potassium phosphate should be added early and calcium gluconate last, or nearly last, to ensure a dilute phosphate concentration.[27] To obtain a homogenous mixture, the solution should be thoroughly agitated after the addition of each ingredient. An appropriate filter should be used for administration of PN to capture precipitates that may have formed in the solution.[27]

Another consideration in PN solutions is the potential for aluminum toxicity. Aluminum is a common element in the environment and is therefore frequently ingested or inhaled.[30] The gastrointestinal tract and lungs provide effective barriers against systemic absorption of aluminum.[30,31] Aluminum is introduced as a contaminant into parenteral drug products during the manufacturing process or from leaching during sterilization of glass containers.[32] When these parenteral products are administered to patients, the aluminum bypasses the body's normal barriers and enters the systemic circulation where it can accumulate in bone and tissues and cause toxic effects.[30,31] Many of the products used in PN are contaminated with aluminum. The combination of multiple products contaminated with aluminum in PN admixtures as well as the sometimes prolonged duration of administration of these mixtures means that patients who receive PN are at risk for developing aluminum toxicity. Certain patient populations, in particular neonates and patients with renal insufficiency, are at a higher risk of accumulating toxic levels of aluminum.[30,31] Sequelae of aluminum accumulation include: decreased bone formation, osteomalacia and fractures; impaired neurological development and encephalopathy; and microcytic hypochromic anemia.[30,31,33]

In 1990, the FDA published a notice of intent expressing concerns about aluminum contamination of TPN solutions and requesting comments on this issue. A final rule on aluminum in large and small volume parenteral products used in TPN was published in 2000.[31] The rule required that the aluminum content of all large-volume parenteral (LVP) products used in TPN, such as amino acid solutions, concentrated dextrose solutions and lipid emulsions, be limited to 25 mcg/L and that the package insert for these LVPs state that the product contains no more than 25 mcg/L of aluminum.[31] For small-volume parenteral (SVP) products and pharmacy bulk packages (PBPs) used in TPN, including electrolyte solutions such as calcium chloride, calcium gluconate, potassium phosphate and sodium phosphate, the product's maximum aluminum level as expiry must be on the container label.[31] The maximum aluminum level may be the highest level obtained for batches produced over the past 3 years or the latest 5 batches.[31] When the rule was enacted, the highest aluminum level could also be the maximum level obtained historically, but this only applied until completion of production of the first 5 batches after the effective date of the rule. The rule also requires that the package insert for all LVPs, SVPs and PBPs contain a warning stating that the product contains aluminum, which may reach toxic levels with prolonged parenteral administration.[31] The warning states that the concern for aluminum toxicity is particularly high in neonates and patients with impaired renal function and that these patients may develop signs of central nervous system and bone toxicity if they receive greater than 4-5 mcg/kg/day of aluminum parenterally.[31] One comment received in response to the imposition of a maximum aluminum intake suggested that the proposed limit would "either make TPN formulations unavailable to neonates or expose doctors to liability, because it is a difficult level to meet."[31] Another comment expressed concern that the proposed limit would not allow patients to

receive appropriate amounts of calcium and phosphates. This has been an ongoing concern in PN formulations for neonates.

The calcium salt recommended for use in PN, calcium gluconate, has "been consistently identified as the calcium (Ca) additive with the highest level of Al [aluminum] contamination in PN."[32] Until recently, calcium chloride was the only parenteral calcium product available in the US that could be used to provide adequate calcium supplementation and limit aluminum contamination in neonatal PN.[32] In a 2012 study, Migaki *et al* stated that calcium chloride and sodium phosphate had been used in neonatal PN formulations containing TrophAmine® (10% amino acid injection) at their hospital (Providence St. Vincent Medical Center in Portland, Oregon) since 2000.[33] These authors evaluated the maximum concentrations of calcium chloride and sodium phosphate that could be used in TrophAmine®-based solutions as well as the aluminum concentration in solutions containing calcium chloride and sodium phosphate, calcium gluconate and sodium phosphate, and calcium gluconate and potassium phosphate. Aluminum concentration of the final solutions was calculated based on manufacturer's information on maximum aluminum content and measured using mass spectrometry. The mean measured aluminum concentrations for solutions containing calcium chloride and sodium phosphate, calcium gluconate and sodium phosphate, and calcium gluconate and potassium phosphate were 6.0 mcg/dL, 22.9 mcg/dL and 31.5 mcg/dL, respectively. The authors found that they were able to meet recommended parenteral intake of calcium (60-80 mg/kg/day) and phosphorus (45-60 mg/kg/day) while still limiting aluminum exposure with PN solutions containing calcium chloride and sodium phosphate administered at rates ≥ 120 mL/kg/day. Below this rate, calcium administration would be below the recommended intake for neonates. The authors concluded that substituting calcium chloride and sodium phosphate for calcium gluconate and potassium phosphate in PN solutions can reduce aluminum exposure to near FDA guidelines for neonatal patients, but further studies are necessary to determine the long-term effects of these substitutions.

In 2014, Huston *et al* published a precipitation study investigating the use of calcium chloride and potassium phosphate in PN solutions containing TrophAmine® or Premasol (amino acid injection).[32] The authors found that "while $CaCl_2$ is the preferred additive that is available in North America when attempting to reduce Al [aluminum] intake to levels near recommended limits, Ca [calcium] and Phos [phosphate] administration will often be below recommended levels due to the need to limit the concentration of Ca and Phos in PN solutions containing CaCl2 and phosphates."[32] They suggested that a better alternative than calcium chloride, such as calcium gluconate in plastic vials, is needed for calcium supplementation in neonatal PN. Calcium gluconate in plastic vials became available after the publication of this study.

In 2017, Huston *et al* conducted an experiment exploring the aluminum concentration in TrophAmine®-based PN solutions containing calcium chloride and sodium phosphate, calcium gluconate from glass vials and sodium phosphate, and calcium gluconate from plastic vials and sodium glycerophosphate.[34] For each combination of calcium and phosphate, multiple solutions were compounded with and without cysteine. The aluminum concentrations of the final solutions were calculated from the aluminum content provided by the manufacturer for each component and measured using inductively coupled plasma/mass spectrometry. The mean measured aluminum concentrations for solutions without cysteine containing calcium chloride and sodium phosphate, calcium gluconate from glass vials and sodium phosphate, and calcium gluconate from plastic vials and sodium glycerophosphate were 2.2 mcg/dL, 14.6 mcg/dL and 1.3 mcg/mL, respectively. The mean measured aluminum concentrations for solutions with cysteine containing calcium chloride and sodium phosphate, calcium gluconate from glass vials and sodium phosphate, and calcium gluconate from plastic vials and sodium glycerophosphate were 2.3 mcg/dL, 15.1 mcg/dL and 1.5 mcg/dL,

respectively. The authors concluded that "the recent introduction of CaGluc-Pl [calcium gluconate in plastic vials] into the United States provides another option, in addition to $CaCl_2$, for limiting the Al [aluminum] exposure from PN of neonatal patients to levels within the FDA guideline."[34] However, the authors observed, the best option for reducing aluminum contamination and the risk of calcium/phosphate precipitation in PN, sodium glycerophosphate, is still not routinely available in the US.

A recent search (April 19, 2021) of the FDA Drug Shortages Database returned no results for sodium phosphate.[35] A search of the American Society of Health-System Pharmacists (ASHP) list of current drug shortages returned a resolved shortage for sodium phosphate injection from December 9, 2020.[36] The reason provided for the shortage was American Regent, Inc. was not currently marketing sodium phosphate injection; sodium phosphate injection remained available from other manufacturers. In the presence of parenteral electrolyte product shortages, ASPEN recommended that clinicians provide oral or enteral phosphate supplementation whenever possible.[37] In addition, ASPEN recommended that electrolyte additives in IV fluids be limited to those patients who need them and to use premixed IV electrolyte products if possible. If there is a shortage of injectable electrolyte products, then ASPEN suggested that clinicians consider reducing the amount of or discontinuing electrolytes added to PN and utilizing premixed PN products. ASPEN also suggested that clinicians consider using IV fat emulsions, which contain phosphate as egg phospholipids, or organic phosphate injections, such as sodium glycerophosphate, in the event of a shortage of injectable inorganic phosphate products.[37,38] During the recent sodium phosphate injection shortage, Fresenius Kabi provided Glycophos® (sodium glycerophosphate) to the US in an attempt to alleviate the phosphate injection shortage.[36]

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

No combination products were nominated

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. Eight SMEs discussed sodium phosphate. Six of these SMEs discussed sodium phosphate during interviews conducted in project Year 3; 2 SMEs discussed sodium phosphate during interviews conducted in project Years 2 and 3. All 8 SMEs were pharmacists. The SMEs specialized and/or were board-certified in nutrition, working in academic medical institutions, hospitals, and an outsourcing facility. The SMEs had been in practice for 8 to 43 years.

Sodium phosphate was nominated as an IV solution for electrolyte supplementation. Most of the SMEs preferred to use sodium phosphate, versus potassium phosphate, in PN formulations for both adult and pediatric patients. In adults, sodium phosphate was preferred unless a patient's potassium levels were low, in which case, potassium phosphate would be utilized. Sodium phosphate was added to PN formulations for pediatric patients because it is less contaminated with aluminum than potassium phosphate. One SME stated:

> In our approach at least, when it comes to parenteral nutrition, in general, if it was safe and reasonable to do otherwise, we typically default to sodium phosphate or encourage it. And the main reason is that the potassium phosphate generally has a little bit more aluminum contamination in these patients on PN, especially over long-term.

Another SME commented, "The benefit of using sodium phosphate really is only going to be seen in probably children less than one year of age and part of it's because potassium phosphate has three times the amount of aluminum that's in sodium phosphate." One SME suggested that the potassium provided with administration of potassium phosphate is also a concern, saying:

> So sodium phosphate historically has less aluminum contamination in it. And aluminum is bad for our baby bones. And additionally, we don't like those extra sources of K [potassium]. So the standard concentration, one is 1.5 mEq for every millimole of phosphorus. And so, having that extra K in there bites us in the butt, because sometimes our kids don't pee.

This SME also said:

> I do have some neonatologists who like them some K phos [potassium phosphate] because they think the kid's peeing and they're afraid they're going to get dehydrated and get hypernatremic. So some people do like it, but not as much as sodium phosphate. Sodium phosphate would be the primary one in pediatrics.

One SME observed that since potassium phosphate is now packaged in plastic vials, aluminum contamination is less of a concern with these products and the choice of sodium phosphate or potassium phosphate depends on the clinical situation. Another SME shared, "I used potassium phosphate in adults

routinely and didn't really have an issue. The sodium phosphate never affected me from the adult side." One SME remarked:

> I think it's basically a clinical choice. We used to teach all of our residents that you use K phos [potassium phosphate] because, thinking about the nutritional electrolytes, the intracellular electrolytes they're going to be potassium and phosphorus. And you would think that a lot of their needs would go hand in hand, plus extra needs go hand in hand as well. You're thinking about respiratory metabolic alkalosis causing hypophosphatemia as well. So it just kept it simpler for us.

When asked about phosphorus doses in PN or supplementation in IV fluids, one SME said that they use an electrolyte protocol at their facility. This protocol recommends phosphorus doses in increments of 15, 30 and 45 mmols and according to the SME:

> It's rare that you would get above that amount. Certainly, I would not recommend above that without at least rechecking serum levels first, and then potentially you might need more repletion after that, but I can't recall ever seeing or recommending a dose more than 45 millimoles for an adult with normal renal function without checking.

This SME hypothesized that more concentrated phosphorus products might be useful in patients who require fluid restriction, but the reduction in volume from such products would be negligible in an adult. The SME also noted that compatibility becomes a concern with more concentrated phosphorus products.

Three SMEs suggested that there is a need for injectable organic phosphorus products, specifically sodium glycerophosphate. The use sodium glycerophosphate in PN formulations would reduce the risk of calcium and phosphorus precipitation. One SME commented:

> We never went to glyco-phos [sodium glycerophosphate], and we would have liked to try it. That was the European product that allows you to put more calcium and phosphorus in the solution together. For a neonate, I cannot give you enough calcium and phosphorus. Mom's placenta was 100 times better than my bag. There are things we'd love to try but we haven't gotten to because it's not approved by the FDA.

This SME also said:

> Now I will say, I'm jealous those people that got to use the sodium glycerol phosphate. That was supposedly some good stuff that it was very soluble. That would be the greatest thing ever, because then I could get more calcium and phos [phosphorus] into my TPN and help my bones and they would be better overall.

Two SMEs perceived a need for preservative-free phosphorus products. These SMEs thought that preservative-free products might be important for critically ill patients, in particular pediatric patients, who routinely receive multiple IV medications. One SME commented, "It's cumulative, so you look at the whole big picture. If it's one ingredient, it's not going to be a problem, but if everything you add has a lot of preservatives in, it becomes a problem. Benzyl alcohol is a big one for us." This SME also noted that some patients have allergies that necessitate the use of preservative-free products. Another SME noted, "I don't think with parenteral nutrition additives, for our combines, we use anything that has preservatives in it. That's really used for something that's on the floor, that you're going to go into the vial a couple of times a day."

Several of the SMEs had experienced shortages of phosphorus products. During such shortages, the SMEs reserved sodium phosphate for use in neonates due to concerns about aluminum contamination in potassium phosphate products. The SMEs expressed a desire for multiple sources of both sodium

phosphate and potassium phosphate, which would allow for more flexibility if one or both substances were not available. One SME remarked:

> But there was a pretty severe shortage. I think it was sodium phosphate for quite a while. Having to use potassium phosphate and I know it was an issue in the neonates, so yeah I think given shortages, there's always a benefit to being able to have something readily compoundable. Yeah. It would be nice to have multiple sources of the product.

Overall, the SMEs expressed a preference for sodium phosphate products. Due to the occurrence of shortages of phosphorus products and the need to use sodium phosphate in certain populations, SMEs thought there was a need for several sources of sodium phosphate and potassium phosphate.

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 sodium phosphate 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 sodium phosphate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded sodium phosphate

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded sodium phosphate

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
Sodium phosphate	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

Sodium phosphate was nominated for inclusion on the 503B Bulks List an IV solution. Sodium phosphate is available as an FDA-approved monobasic and dibasic injectable product. Sodium phosphate is also available in the nominated dosage form and ROA in Abu Dhabi and Saudi Arabia.

Sodium phosphate is a component of an FDA-approved product that is currently available. The nominated product did not differ substantially from the commercially available product. Therefore, a systematic literature review was not conducted. A search for background information on hypophosphatemia and the use of injectable sodium phosphate revealed that low phosphorus may occur with many conditions, such as primary or secondary hyperparathyroidism, vitamin D deficiency, refeeding syndrome or use of certain medications. Acute, severe hypophosphatemia requires IV phosphorus for repletion and ongoing supplementation. Phosphorus is also administered in PN formulations. The source of calcium and phosphorus in a PN formulation affects the risk precipitate formation and aluminum contamination in the mixture. Inorganic salts, such as calcium chloride, sodium phosphate and potassium phosphate, dissociate more extensively than organic salts, such as calcium gluconate and sodium glycerophosphate, thereby providing more substrate to form calcium phosphate compounds. Since sodium glycerophosphate is not approved for use in the US, sodium phosphate is often used as the source of phosphorus in PN because sodium phosphate products tend to be less contaminated with aluminum than potassium phosphate products (although the risk of aluminum contamination is reduced when potassium phosphate in plastic vials is utilized) and solubility curves are available for this substances and calcium products.

Most of the SMEs who were interviewed typically used sodium phosphate rather than potassium phosphate in PN formulations. This preference for sodium phosphate was due to concerns about aluminum contamination of potassium phosphate, and the potential for aluminum accumulation, particularly in pediatric patients. One SME noted that aluminum contamination is less of a concern now that potassium phosphate is packaged in plastic vials, which means the choice of phosphorus product depends on the clinical situation. Some SMEs expressed concerns about providing excess potassium with the use of parenteral potassium phosphate. Several SMEs had experienced shortages of electrolyte products, including phosphorus. These SMEs indicated that, due to frequent shortages, there was a need for multiple sources of both sodium phosphate and potassium phosphate products. Three SMEs were interested in having sodium glycerophosphate available in the US as an approved product.

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

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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 sodium phosphate to your patients?
    - Yes
    - No
3. Do you prescribe or administer sodium phosphate 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 sodium phosphate for the following conditions or diseases: (check all that apply)
    - Hypophosphatemia
    - Other (please explain) _____
5. I prescribe or administer sodium phosphate with my patients as the following: (check all that apply)
    - FDA-approved drug product
    - Compounded drug product
    - Other (please explain) _____
6. I use compounded sodium phosphate 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 sodium phosphate
    - Other (please explain) _____
7. Do you stock non-patient-specific compounded sodium phosphate at your practice?
    - Yes
    - No
    - I'm not sure
8. I obtain compounded sodium phosphate 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) _____

9. 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) _____
10. 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
    - Sodium phosphate
    - Methylprednisolone
    - Midazolam
    - Mupirocin
    - Norepinephrine
    - Ondansetron
    - Phytonadione
    - Sodium phosphate
    - 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.