Summary Report

Potassium 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

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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

API	Active Pharmaceutical Ingredient
ASHP	American Society of Health-System Pharmacists
ASPEN	American Society of Enteral and Parenteral Nutrition
EMA	European Medicines Agency
EKG	Electrocardiogram
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
ISMP	Institute for Safe Medication Practices
IV	Intravenous
OTC	Over-the-counter
NPSG	National Patient Safety Goal
REMS	Risk Evaluation and Mitigation Strategy
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States
USP	United States Pharmacopeia
WHO	World Health Organization

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of potassium chloride (UNII code: 660YQ98I10), 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 potassium 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 potassium 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 potassium 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

Potassium chloride was nominated for inclusion on the 503B Bulks List by Cantrell Drug Company, Specialty Sterile Pharmaceutical Society (SSPS), and US Compounding Pharmacy.

Potassium chloride was nominated for prevention and treatment of hypokalemia via an intravenous (IV) injection solution. Two nominators specified a preservative-free solution in concentrations of 20 mEq/100 mL and 40 mEq/mL. One nominator specified IV solutions in concentrations ranging from 2 mEq/mL to 40 mEq (volume not provided).

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of potassium chloride.[6-14]

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.
- Premixed solutions reduce the risk of ampule glass shards contamination or direct infusion of concentrate accidents.

METHODOLOGY

Background information

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

Potassium chloride is currently available as FDA-approved injectable products. 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 potassium 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 potassium 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 potassium 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

- Potassium chloride is available as an FDA-approved product in the nominated dosage form and ROA. Potassium chloride is also available as an FDA-approved oral capsule, solution, and tablet.
- Potassium chloride is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for potassium chloride.
- Potassium chloride is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, Saudi Arabia, and UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Potassium chloride[c]	0.2-3 mEq/mL 0.5-40 mEq/100 mL	Solution	Injection	Prescription	Approved Prior to Jan 1, 1982

[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.
[c]Includes potassium chloride for injection concentrate and potassium chloride in dextrose, sodium chloride, or dextrose and sodium chloride.

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]
Potassium chloride	0.1-0.4 mEq/mL	Liquid	Intravenous	Canada	Ethical	8/10/2000
	1-4 mEq/mL	Concentrated solution	Infusion	Abu Dhabi	Active	–
			Injectable	Hong Kong	Prescription-only	6/1/1979
				Namibia	–	1/1/1978
			Intravenous	Australia	Not scheduled	7/9/1991
				Belgium	Medical prescription	4/30/1971
				Canada	Ethical	12/31/1951
				Ireland	Prescription-only, non-renewable	11/18/1988
				Latvia	Prescription	12/28/1999
				New Zealand	General Sale	10/31/1996
				Saudi Arabia	Prescription	–
				United Kingdom	Prescription-only	12/1/1986
	0.5-20 mEq/100 mL	Solution	Injectable	Abu Dhabi	Active	–

				Hong Kong	Prescription-only	12/13/1994
				Namibia	–	1/1/1978
			Intravenous	Australia	Not scheduled	9/30/1991
				Belgium	Medical prescription	7/6/2003
				Canada	Ethical	12/21/1979
				Ireland	Prescription-only, non-renewal	7/27/2012
				New Zealand	General sale	929/1980
				Saudi Arabia	Prescription	–
				United Kingdom	Prescription-only	10/31/2001

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.

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 potassium chloride.

Potassium is the most abundant intracellular cation in the human body, with 98% found in the intracellular space and only 2% in the extracellular space.[15] Potassium is critical to the function of cells throughout the body, playing a role in maintaining acid-base balance, isotonicity, electrical gradients across membranes and metabolism.[16] The potassium gradient between the intracellular and extracellular space creates an electrical action potential across cell membranes, which nerve and muscle cells rely upon for conduction and contraction.[15,17] The sodium-potassium ATPase pump found in the membrane of almost all cells maintains this gradient by moving potassium into cells and sodium out.[15,18,19] Insulin and catecholamines enhance potassium influx into cells by increasing activity of the sodium-potassium ATPase pump.[20]

Potassium homeostasis is a balance between dietary intake and renal and gastrointestinal excretion.[15,21,22] Dietary sources of potassium include dried fruit, nuts, avocados, bran cereals, fruits (bananas, cantaloupe, kiwis, oranges), vegetables (spinach, tomatoes, broccoli, carrots, beets) and meat.[23] Approximately 80% of potassium is excreted via the kidneys, 15% via the gastrointestinal tract and 5% in sweat.[15,23] At least 90% of the potassium filtered by the glomerulus is reabsorbed in the proximal tubule and ascending limb of Henle.[15,20] The kidneys are the major site of potassium regulation in the body. Elevated potassium stimulates aldosterone release via the renin-angiotensin-aldosterone system or directly from the adrenal cortex.[17] Aldosterone promotes potassium excretion along the distal nephron.[20]

Normal serum potassium levels are 3.6 to 5.0 mmol/L.[23] Hypokalemia is defined as serum potassium less than 3.5 mmol/L, with mild hypokalemia in the range of 3.0-3.5 mmol/L, moderate hypokalemia in the range of 2.5-3.0 mmol/L and severe hypokalemia less than 2.5 mmol/L.[24,25] Hypokalemia develops due to decreased potassium intake, increased intracellular uptake and/or increased renal or gastrointestinal loss.[17,23-25] Decreased dietary intake alone rarely leads to hypokalemia, although it may over time.[20,24] More often, decreased potassium intake exacerbates hypokalemia. Shift of potassium from the extracellular to intracellular space, due to endogenous or exogenous insulin or catecholamines, alkalosis, or certain drugs or toxins, can contribute to or cause hypokalemia.[20,22,23] Increased renal potassium loss may occur due to: primary or secondary hyperaldosteronism; Cushing's disease; renal tubular disorders or damage; congenital or genetic disorders; or hypomagnesemia. Prolonged vomiting or diarrhea, malabsorption, nasogastric suctioning and laxative abuse may cause excessive loss of potassium via the gastrointestinal tract.[17,18,26] Many medications are associated with hypokalemia. Beta-adrenergic agonists, such as albuterol, epinephrine, isoproterenol and terbutaline, stimulate shift of potassium to the intracellular space. Insulin, theophylline and caffeine also promote shift of potassium from the extracellular to intracellular space.[23,27] Diuretics, including acetazolamide, furosemide and thiazides, are one of the most common causes of hypokalemia, potentiating renal potassium excretion. Some antibiotics, such as ampicillin, penicillin and aminoglycosides, also contribute to renal potassium loss.[27] Corticosteroids, such as hydrocortisone and prednisone, increase renal potassium loss through their effect on glomerular filtration rate and distal sodium delivery.[23,27] Mineralocorticoids, such as fludrocortisone, also enhance renal potassium loss.

Refeeding syndrome is a condition associated with imbalances of several electrolytes, including potassium. 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."[28] 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 such as the sodium-potassium ATPase pump, resulting in leakage of potassium into the circulation. This leakage of potassium into the extracellular space helps maintain serum potassium levels in the normal range, despite decreased dietary intake. However, some of the leaked potassium is filtered and excreted by the kidneys.[28] 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.[28,29] 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.[28] Insulin also increases sodium reabsorption from the distal nephron, which leads to water retention and potentially fluid overload.[28,29]

Clinical signs of hypokalemia are proportional to the degree and duration of potassium depletion.[17,24] Signs do not typically manifest until serum potassium levels drop below 3.0 mmol/L, unless there is an acute rapid decrease in potassium or a potentiating factor, such as digitalis use.[17,24] Thus, chronic mild hypokalemia is often asymptomatic in otherwise healthy individuals. Many of the signs and symptoms associated with hypokalemia are related to membrane hyperpolarization in the presence of low extracellular potassium, leading to less sensitivity to excitation in nerve and muscle cells and subsequently, neuromuscular weakness.[15,20] This neuromuscular weakness usually starts in the lower limbs and ascends to the trunk, upper extremities and muscle of respiration.[24] Severe hypokalemia can cause muscle cramps, rhabdomyolysis, paralysis and eventually, respiratory failure.[15,17,24-26] In the gastrointestinal system, limited smooth muscle contractions leads to constipation and ileus.[17,26] Chronic hypokalemia "can cause structural and functional changes in the kidney that include impairing concentrating ability, increased ammonia production, altered sodium reabsorption and increased bicarbonate absorption" resulting in polyuria and polydipsia.[24] Perhaps the most emergent sequelae occurs in the cardiovascular system, where hypokalemia increases the risk of cardiac arrhythmias and accompanying changes on electrocardiogram (EKG), cardiac arrest and heart failure.[15,20,24,26] These sequelae are particularly concerning in patients with preexisting heart disease because these patients often have diuretic-induced hypokalemia and may already be at a higher risk for adverse cardiovascular events due to their underling condition.

In the outpatient population, mild hypokalemia occurs in almost 14% of patients undergoing lab testing.[17] Hypokalemia is detected in approximately 20% of hospitalized patients.[17,30] A 2018 meta-analysis evaluating the relationship between abnormal potassium levels and mortality across a range of kidney function found that the prevalence of serum potassium < 4.0 mmol/L was 23.57% and 12.61% in the general population/high cardiovascular risk cohorts and chronic kidney disease cohorts, respectively. The prevalence of serum potassium < 3.5 mmol/L was 1.91% and 2.03% in the general population/high cardiovascular risk cohorts and chronic kidney disease cohorts, respectively.[31] The analysis included 27 international cohorts in the Chronic Kidney Disease Prognosis Consortium with a total of 1,217,986 participants followed for an average of 6.9 years. The average baseline potassium was 4.2 ± 0.4 mmol/L. Risk factors for hypokalemia in the general population/high cardiovascular risk cohorts included: younger age; female gender; Black race; higher systolic blood pressure; thiazide or loop diuretic use; lower serum cholesterol; lower body mass index; and higher

urine albumin-to-creatinine ratio. Factors that protected against hypokalemia in the general population/high cardiovascular risk cohorts included: use of an angiotensin-converting enzyme inhibitor or potassium-sparing diuretic; diabetes mellitus; and history of coronary heart disease or stroke. Risk factors for hypokalemia in the chronic kidney disease cohorts were "generally consistent in direction if weaker" than those in the general population/high cardiovascular risk cohorts, with the exception of the use of renin-angiotensin-aldosterone system inhibitors which had a stronger protective effect in the chronic kidney disease cohorts.[31] The lowest risk of all-cause mortality occurred when serum potassium was between 4 mmol/L and 4.5 mmol/L; higher risk of all-cause mortality occurred outside of the 3.5 to 5.0 mmol/L range. The overall adjusted hazard ratio for all-cause mortality at serum potassium of 3.0 mmol/L and 5.5 mmol/L was 1.49 (95% confidence interval 1.26-1.76) and 1.22 (95% confidence interval 1.15-1.29), respectively; the "Risk relationships were similarly U-shaped for CV [cardiovascular] mortality and end-stage renal disease."[31] The authors concluded that "Hypo- and hyperkalaemia are independently associated with significantly higher all-cause and CV [cardiovascular] mortality, and with higher risk of ESRD [end-stage renal disease], with the best outcomes seen with serum potassium levels of 4–4.5mmol/L" and further research is needed "to determine whether the correction of abnormal serum potassium levels can result in improvement in mortality and delayed onset of dialysis."[31]

Chronic kidney disease is often associated with hyperkalemia, however hypokalemia can also occur in these patients. The prevalence of serum potassium less than 3.5 mmol/L was 3% in a study of 36,359 patients with chronic kidney disease.[32] In a 2019 systematic review and meta-analysis, Zhang *et al* examined the association between hypokalemia and all-cause mortality in patients with chronic kidney disease with or without dialysis.[33] Eleven studies with 57,234 patients were included, with a mean follow-up of 4.1 years. Ten of these studies evaluated the association between low serum potassium and all-cause mortality. Meta-analysis showed that patients with serum potassium less than 4 mmol/L had a higher risk of all-cause mortality (hazard ratio, 1.57; 95% confidence interval, 1.25-1.97), although there was significant heterogeneity across studies. Four studies considered the relationship between serum potassium less than 3.5 mmol/L and all-cause mortality. Meta-analysis revealed a significantly higher risk of all-cause mortality in patients with serum potassium less than 3.5 mmol/L (hazard ratio, 2.05; 95% confidence interval, 1.86-2.25).

Hypo- and hyperkalemia have also been associated with a higher risk of mortality in patients with heart disease. A 2019 meta-analysis exploring the association between potassium and mortality from acute myocardial infarction found that patients with lower or higher serum potassium levels had a higher risk of mortality.[34] In patients with serum potassium less than 3.5 mmol/L, the pooled relative risk for morality was 1.15 (95% confidence interval, 1.00-1.32). In a recent retrospective study, Alfano *et al* determined the prevalence, risk factors and outcome for hypokalemia in a cohort of 290 patients with coronavirus disease 2019 (COVID-19). One hundred nineteen patients (41%) had documented hypokalemia, which was mild in the majority of patients; the mean serum potassium was 3.1 ± 0.1 mmol/L. Analysis showed that female sex and diuretic therapy were significantly associated with hypokalemia. Hypokalemia, when adjusted for sex, age and Sequential Organ Failure Assessment (SOFA) score, was not associated with transfer to the intensive care unit, in-hospital mortality, or composite outcome of intensive care unit transfer or in-hospital mortality. Patients received oral (28 patients, 23.5%), intravenous (14, 11.7%) and oral and intravenous (1, 0.8%) potassium supplementation.

The goals of therapy in patients with low potassium are to avoid or resolve symptoms of hypokalemia, return serum potassium concentration to normal range, and prevent hyperkalemia.[15] No pharmacological therapy is necessary in patients with low-normal serum potassium (3.5-3.9

mmol/L).[27] Low-normal serum potassium is often seen in patients with heart disease who are receiving diuretics. In these patients, the dose of non-potassium sparing diuretics should be either reduced or eliminated entirely and replaced with loop diuretics.[21,23] Potassium binders should also be discontinued, and the diet assessed for possible ways to increase potassium intake. Increasing dietary potassium alone is not an effective method of increasing serum potassium because the potassium in most foods is coupled with phosphate and potassium loss is typically associated with concurrent chloride depletion.[23,24,30] In a 2020 state-of-the-art review on potassium abnormalities in patients with heart failure, the authors recommended that a mineralocorticoid receptor antagonist should be started in patients diagnosed with low-normal potassium, or if the patient is already receiving a mineralocorticoid receptor antagonist, then the dose should be increased.[21] The authors of this review stated that normalization of potassium in patients with heart failure, particularly with a mineralocorticoid receptor antagonist, is associated with better outcomes. The authors of this review also recommended that the dose of angiotensin-converting enzyme inhibitors and/or angiotensin receptor-neprilysin inhibitors be increased in patients with hypokalemia.

Patients with mild to moderate hypokalemia are usually asymptomatic and therefore, do not require urgent potassium repletion.[24,26] Oral potassium supplementation is recommended for these patients. Potassium chloride is preferred for potassium supplementation because, as mentioned above, potassium loss is usually accompanied by chloride depletion. Oral supplementation is preferable to IV because the relatively slow gastrointestinal absorption of potassium reduces the possibility of an abrupt, large increase in serum potassium and rebound hyperkalemia.[16,24] Recommended daily doses for oral potassium supplementation in patients with mild to moderate hypokalemia range from 40 to 100 mmol per day.[17,23,28,30] Oral potassium supplements may irritate the gastrointestinal mucosa, resulting in nausea, vomiting, abdominal pain and occasionally, ulceration.[23,24] If a patient with mild to moderate hypokalemia cannot tolerate oral or enteral potassium supplementation, has changes on EKG consistent with hypokalemia, or is otherwise symptomatic, then IV potassium may be provided.

IV potassium administration is recommended for patients with severe hypokalemia (less than 2.5 mmol/L). As with oral administration, potassium chloride is preferred for IV supplementation "because of its unique effectiveness against the most common causes of potassium depletion."[23] Potassium bicarbonate or acetate may be utilized if acidemia is present; potassium phosphate may be used if the patient is both hypokalemic and hypophosphatemic.[15] Every 0.3 mmol/L decrease in serum potassium level is equivalent to a 100 mmol reduction in total body potassium; this relationship can be used to calculate an approximate potassium deficit.[30] In patients with mild to moderate hypokalemia and normal renal function, the IV potassium replacement dose is 20 to 40 mmol.[15,29] In patients with severe hypokalemia and normal renal function, the IV potassium replacement dose is 40 to 80 mmol.[15,29] Total daily potassium supplementation should not exceed 240 to 400 mmol.[15] The recommended potassium dose for children with hypokalemia is 0.5 to 1 mmol/kg/day, with a maximum of 40 mmol.[30] The American Society of Parenteral and Enteral Nutrition (ASPEN) recommends a potassium dose of 1 to 2 mmol/kg/day for adults and children or adolescents > 50 kg receiving parenteral nutrition, with adjustments for excess potassium loss with vomiting, diarrhea, nasogastric suctioning, medications and/or refeeding.[35] The ASPEN recommended potassium dose for preterm neonates and infants or children is 2 to 4 mmol/kg/day.[35] The standard infusion rate for potassium chloride is 10 mmol per hour; the maximum infusion rate is 20 mmol per hour, although rates up to 40 mmol per hour have been used in critical situations.[15-17,26-28,30] If the infusion rate is greater than 10 mmol per hour, then continuous cardiac monitoring is recommended because higher doses of potassium chloride increase the risk of hyperkalemia and cardiac complications.[24,26] Serum electrolytes levels should be checked regularly while a patient is

receiving IV potassium chloride. Potassium chloride must be diluted prior to administration, preferably in 0.9% saline.[15] Although dextrose solutions can be used as diluents, this is not recommended because glucose administration stimulates insulin release, which may exacerbate the hypokalemia.[15,17,30] The recommended concentration for potassium chloride solutions is 20 to 40 mmol/L. Potassium chloride is caustic and may cause pain and phlebitis if administered via a peripheral vein at higher rates and/or concentrations.[15,24] The authors of several reviews on the management of hypokalemia expressed a preference for premixed IV potassium chloride infusions.[17,27]

In addition to being used to correct or prevent hypokalemia, injectable potassium chloride is also used in cardioplegic solutions to induce cardiac arrest.[36] Cardioplegia, the "elective, rapid and reversible paralysis of the heart during cardiac surgery" provides a motionless and bloodless field while preventing myocardial ischemia and reperfusion injury during cardiac procedures that require cardiopulmonary bypass.[37] Cardioplegic solutions vary in their compositions, and different clinicians and institutions express a preference for different solutions.[36] Although the composition of cardioplegic solutions vary, a high concentration of potassium delivered in a crystalloid or blood carrier solution remains a constant.[38,39] The high potassium concentration in these solutions increases extracellular levels of potassium, which alters cell membrane potentials, thereby affecting depolarization. The high potassium concentration maintains the membrane potential above the threshold necessary to open voltage-gated sodium channels, which prevents excitation and contraction, leading to depolarized arrest.[38,39] Cardioplegic solutions contain other electrolytes and additives to facilitate cardiac arrest and protect the heart during ischemia and reperfusion.

Potassium chloride for injection concentrate is on the Institute of Safe Medication Practices (ISMP) list of high-alert medications in acute care settings.[40] This list of medications that "bear a heightened risk of causing significant patient harm when they are used in error" was developed based on error reports submitted to the ISMP National Medication Errors Reporting Program, published reports of errors, studies that identified drugs often involved in errors, and discussions with healthcare practitioners and safety experts. Mistakes with medications on the high-alert medications list are not necessarily more common, but the consequences are more serious. A 1999 Sentinel Event Alert from The Joint Commission described common risk factors for, and made suggestions to prevent, medication errors associated with the use of high-alert medications.[41] Common risk factors for medication errors with concentrated potassium chloride included: storing potassium chloride products outside the pharmacy; mixing potassium chloride solutions extemporaneously; and filling requests for unusual concentrations. The Joint Commission recommended the following to reduce medication errors associated with the use of concentrated potassium chloride: remove concentrated potassium chloride from floor stock; move drug preparation off floor units; use commercially available pre-mixed solutions whenever possible; and standardize and limit concentrations of solutions.

The Sentinel Event Alert was part of an effort in the 1980s and 1990s by the ISMP, United States Pharmacopeia (USP), Institute for Healthcare Improvement and The Joint Commission to bring attention to the dangers associated with the use of concentrated potassium chloride.[10,42] In 1987, the FDA and USP mandated that concentrated potassium chloride be packaged with black caps and closures and carry a warning label to avoid confusion with other parenteral products.[10] A few years later, in 1991, injectable potassium chloride's official USP name was changed to 'potassium chloride for injection concentrate'.[10] In 2000, Abbott Laboratories, at the time the biggest manufacturer of concentrated potassium chloride, stopped packaging potassium chloride for injection concentrate for its Universal Additive Syringe line, precluding administration of undiluted potassium chloride directly into an IV port.[10]

Improving the safety of use of high-alert medications was one of The Joint Commission's first National Patient Safety Goals (NPSGs) in 2002,.[42] The NPSGs were established to help healthcare organizations recognize and improve areas of concern regarding patient safety. These goals and accompanying requirements, which are released on a yearly basis, are part of The Joint Commission's accreditation process for healthcare facilities. The requirements for the goal of improving the safety of medication use were: remove concentrated electrolytes, including potassium chloride, from patient care units; standardize and limit the number of drug concentrations available; and identify and take action to prevent confusion between look-alike/sound-alike drugs.[43] In 2007, The Joint Commission published an annual report with compliance rates for recent NPSGs, derived from 1,573 on-site surveys at Joint Commission accredited hospitals.[43] The compliance rate for removal of concentrated electrolytes from patient care areas was 98.6%. The compliance rate for standardizing and limiting drug concentrations was 98.5%. The compliance rate for identifying and taking action to prevent medication errors with look-alike/sound-alike drugs was 97.6%.

Despite changes in the way concentrated potassium chloride products are labelled, packaged and handled in healthcare facilities, serious errors continue to occur with use of these products. In a 2005 systematic review on best practices for safe handling of concentrated potassium, the authors retrieved no studies that evaluated the effectiveness of measures to improve the safety of using concentrated potassium.[44] The authors therefore made their own recommendations based on expert consensus, their experience at various hospitals and practices encouraged by professional organizations.[44] For drug storage, the authors recommended removing concentrated potassium chloride from clinical areas, storing potassium products in locked cupboards if kept in clinical areas and eliminating the transfer of potassium products between clinical areas. For drug preparation and packaging, providing pre-mixed IV potassium infusions, preparing infusions in the pharmacy and ensuring potassium chloride vials are distinguishable from other injectable products were recommended. Best practices for prescribing and administering potassium products included: prescribing potassium chloride in concentrations available as ready-made infusions; providing oral potassium chloride whenever possible; developing clear therapeutic guidelines for IV infusion rates; and instituting a double-check policy. The authors recommended that the pharmaceutical industry utilize distinct, standardized labelling for potassium products.

Some of these recommendations were echoed in a 2007 aide-mémoire on control of concentrated electrolyte solutions from The Joint Commission and the World Health Organization (WHO) Collaborating Centre for Patient Safety Solutions.[45] The authors stated that "concentrated KCl [potassium chloride] is the most common medication implicated in electrolyte administration errors" and suggested that hospitals, ambulatory care facilities, ambulatory surgery centers, dialysis centers and any other facilities that use concentrated electrolyte solutions in WHO member states remove concentrated potassium products from nursing units or, if this is not possible, store these products in a locked area and individually label each vial with a warning label that states 'Must be diluted'. The authors also suggested that potassium chloride be treated as a controlled substance with restrictions on ordering and requirements for storage and documentation. The authors encouraged member states to recommend that concentrated electrolyte solutions be purchased or prepared in standardized and limited concentrations, that a 'High Risk Warning' label be affixed to these solutions and that an infusion pump be used to administer all such solutions.

In a 2011 article, Grissinger observed that injectable potassium chloride continues to pose a threat to patients.[42] Grissinger identified several situations in which injectable potassium chloride remains easily accessible, including: healthcare facilities where 24-hour pharmacy services are not available and nurses have access to the pharmacy or a night cabinet; availability of potassium in specialty areas,

such as a cardiac bypass suite; and storage in an outpatient setting for preparation of IV solutions or treatments. In this last situation, the outpatient facility may maintain their own stock of potassium chloride without the pharmacy staff's knowledge. Grissinger advised healthcare facilities to perform a failure mode and effects analysis and eliminate unrestricted access to injectable potassium chloride whenever possible. Strategies for reducing access to injectable potassium chloride included: prohibiting nursing access to the pharmacy; using pre-mixed solutions and making them available in a secure area for after-hours use; and requiring that all drugs be purchased through the pharmacy. If potassium chloride is required for cardioplegia, then the vials should be dispensed with bold warning labels and two individuals should verify their delivery.

In a 2014 article, Knox *et al* called for a risk evaluation and mitigation strategy (REMS) for potassium chloride for injection concentrate.[10] The article described a 2001 case in which undiluted potassium chloride was mistakenly administered to a patient via IV push and the patient subsequently died. The authors stated that "administration of potassium chloride for injection concentrate by i.v. push is widely recognized as a 'never event' (i.e., an egregious and preventable medical error) because it is usually fatal."[10] The patient's family sued the hospital; the jury ruled in favor of the family and the verdict was upheld in an appellate court. Knox *et al* presented this case as an example of the risks associated with potassium chloride for injection concentrate and proposed that a REMS would "require prescribers to be educated on the dangers of misuse, and it would necessitate authorization before the dispensing of potassium chloride for injection concentrate so that health care providers could not remove it from the pharmacy without following the proper protocols."[10] Knox *et al* also observed that potassium chloride for injection concentrate is frequently confused with other drugs and emphasized the importance of labeling and packaging in preventing medication errors. These authors recommended that healthcare facilities order potassium chloride for injection concentrate from a different manufacturer than other salt forms of potassium in order to avoid similar labels.

The potential for medication errors due to labeling and packaging may be greater if potassium chloride is obtained from an outsourcing facility because these facilities are not subject to the same labeling requirements as commercial manufacturers.[46] When drugs are ordered from an outsourcing facility, healthcare practitioners may encounter labeling or packaging that is unfamiliar to them, thereby increasing the risk of a medication error. In a 2018 warning about safe handling of concentrated electrolyte products from outsourcing facilities, the National Alert Network provided two examples of how unfamiliar labelling and packaging from outsourcing facilities might lead to confusion amongst practitioners.[46] In the first example, an outsourcing facility provided compounded potassium chloride for injection concentrate in a syringe intended for further dilution in the pharmacy prior to IV administration. Such syringes could mistakenly reach a patient care area and be administered undiluted. In the second example, compounded potassium chloride for injection concentrate was dispensed in a vial with a black cap with 'Must be diluted' but not with a black ferrule bearing this statement. Once the black cap was removed, the potassium chloride for injection concentrate vial looked remarkably similar to a vial of calcium chloride. The National Alert Network pointed out that injectable products obtained from an outsourcing facility may have a label on which the strength per mL is more prominent than the strength per total volume, as required by the FDA and USP for commercial manufacturers. The National Alert Network advised healthcare practitioners to use FDA-approved products whenever possible.[46] If FDA-approved products are not available, then products should be obtained from an outsourcing facility that follows USP labelling standards. Labelling and packaging of products obtained from an outsourcing facility should be evaluated for potential vulnerabilities and steps should be taken to mitigate those vulnerabilities. Pharmacy staff

should communicate with one another and practitioners about drug shortages and differences in product labelling and packaging. Regardless of where potassium chloride for injection concentrate products are obtained from, the National Alert Network cautioned that these products should never leave the pharmacy undiluted.[46]

When the National Alert Network warning was published in May 2018, it suggested that "Given the near total lack of availability of potassium chloride for injection concentrate in vials (2 mEq/mL), along with problems accessing the 250 mL pharmacy bulk package (2 mEq/mL), some healthcare providers have benefitted [*sic*] from outsourcing facilities that have compounded this product starting with the active pharmaceutical ingredient (API)."[46] A recent search (March 26, 2021) of the FDA Drug Shortages Database returned no results for potassium chloride.[47] A search of the American Society of Health-System Pharmacists (ASHP) list of current drug shortages returned a resolved shortage for potassium chloride injection from May 30, 2019.[48] The reasons provided for the shortage were discontinuation of 250 mL bottles of potassium chloride 2 mEq/mL by Pfizer in mid-2018 and discontinuation of potassium chloride 10 mEq/500 mL in 5% dextrose and 0.225% sodium chloride by ICU Medical in 2018. In the presence of injectable potassium chloride shortages, ASHP recommended that clinicians provide oral or enteral potassium supplementation whenever possible. ASHP commented that "compounding potassium-containing products poses significant safety risks."[48] ASPEN also recommended the use of oral or enteral parenteral potassium supplementation if there is a shortage of injectable potassium chloride.[49] In addition, ASPEN recommended that electrolyte additives in IV fluids be limited to those patients who need them and to use premixed IV potassium products if possible. If there is a shortage of injectable electrolyte products, then ASPEN suggested that clinicians consider reducing or discontinuing the amount of electrolytes added to parenteral nutrition.

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 potassium chloride. 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.

Potassium chloride was nominated as an IV solution in various concentrations. The SMEs used injectable potassium chloride in parenteral nutrition mixtures, IV fluid bags and diasylate fluid. One SME indicated that certain patient populations, including cardiac and oncology patients, often require potassium supplementation independent of parenteral nutrition. This SME remarked, "So they go on amphotericin B and some of the transplant drugs, you can't put enough potassium in them…they're using massive amounts of potassium. This is when we get called, because they're exceeding 120 per liter of potassium and it becomes a real issue." Another SME referenced a report that had been done at their hospital that showed that fluid and electrolyte disorders were amongst the most common findings in medical and surgical oncology patients. This SME stated:

> I guarantee you that those [injectable electrolyte solutions] will definitely always be products that will have to be individual products. It will just have to be because, especially in cancer patients, a lot of their therapies are causing a lot of those requirements to be increased. Giving it intravenously a lot of times may be your only option for some of those patients.

Most of the SMEs preferred to use commercially available injectable potassium chloride products and did not see a need for additional concentrations or package sizes. In response to the question of whether or not there is a need for compounding facilities to prepare different potassium chloride products, one SME said, "Well, the only time where we use a 503B facility for repackaging bolus doses." Another SME remarked, "As far as I understand there are plenty of sources for these [potassium chloride products] commercially and I guess I was going to have a backup to the backup and it could be something I'm not thinking of that my colleagues will, but it doesn't seem to be." This SME did not see a need for compounded potassium chloride products in concentrations not currently available, observing, "I think everyone's become comfortable with 20 and 40 or 60 or whatever." Another SME made a similar statement, observing:

> We, whenever possible, use the commercially available products. And there's I think a 10 per 120 and a 40 and a 10 per hundred if we had a personal line, for example and then 20 or 40, only for like a central line. But we, whenever possible, we use the commercially available products and that's just been our approach with compounding drugs, whenever there's a commercial product, just for safety reasons.

Another SME commented that they could see using a compounding facility to obtain potassium chloride products in order to "get better dating, but I wouldn't change concentrations or vial sizes. They pretty much meet the need…". Two SMEs who routinely compounded PN mixtures preferred to use 250 mL bottles of potassium chloride because the larger bottles reduced the need to frequently exchange bottles on the compounder as well as the cost associated with use of small vials. However, both of these SMEs understood that the larger bottles potentially created a lot of waste for facilities that only use the product to make IV bags with potassium chloride and do not compound a high volume of PN because they cannot access the bottle multiple times. Therefore, the large bottles were not cost effective for some facilities. One SME opined that if larger bottles of potassium chloride were readily available, "You'd almost have to make it such that only those products could be sold to a compounding center as opposed to your general

pharmacy, because then you could have so many med errors. Doing it with potassium, I don't know, that's a scary drug to be messing with."

Most of the SMEs had not experienced a shortage of injectable potassium chloride. One SME indicated that larger bottles of potassium chloride may be used when small vials are not available. Another SME thought that only one manufacturer made 100 mL bottles of potassium chloride and remarked, "…those have been on shortage here and there. So that could be a problem." One SME commented that if they need additional potassium chloride at their facility, then they make it onsite. When asked about purchasing premixed IV bags with potassium chloride, one SME observed that facilities weigh the labor costs involved with compounding such products in-house against the cost of purchasing the premixed products. This SME noted that safety also factors into the decision to purchase premixed products because there is less potential for contamination and error with premixed products, which may be particularly important for potassium chloride because it is a high-risk medication.

Several SMEs expressed concerns about the safety of compounded injectable potassium chloride products, suggesting that different concentrations and/or packaging may lead to medication errors. One SME stated:

> There's more than enough manufacturers for that [injectable potassium chloride], and I get concerned if you get different packaging and different concentrations and different stock volumes. And back to the error relationship, with barcoding and stuff with use, it's decreased quite a bit, but you want to put your employees in the best possible position to do their job successfully and to have a wide variety of different products available because they are, or there might be a rare use or, or whatever. But I'd rather keep it simple and keep it safe.

When discussing another nominated substance, potassium phosphate, one SME recalled a presentation that they had heard at a conference several years ago in which the presenter described an incident with the facility that they used to compound all of their PN mixtures. This facility typically used potassium acetate 2 mEq/mL to provide potassium in their PN formulations. During a shortage of injectable electrolyte products, they were only able to obtain potassium acetate 4 mEq/mL. No one noticed the difference in concentration. The higher concentration product was added to PN formulations in the same volume as had been used for the lower concentration product for one month before physicians began questioning why their patients were hyperkalemic. Someone reviewed the compounding records at the facility and detected the difference in concentration between the two potassium acetate products.

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 potassium 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 potassium chloride prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded potassium chloride

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded potassium 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
Potassium 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

Potassium chloride was nominated for inclusion on the 503B Bulks List for prevention and treatment of hypokalemia via IV injection solution. Potassium chloride is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, Saudi Arabia, UK and the US.

Due to the availability of FDA-approved products in the nominated ROA and dosage form, a literature review was not conducted. Several studies were identified that provided information about the clinical use of potassium chloride. Patients with mild to moderate hypokalemia are usually asymptomatic and, depending on the patient's condition and the underlying cause of the hypokalemia, can often be treated with oral potassium supplementation. IV potassium administration is recommended for patients with severe hypokalemia. Injectable potassium chloride is also used in cardioplegic solutions to induce cardiac arrest. Potassium chloride for injection concentrate is on the ISMP list of high-alert medications in acute care settings. In the 1980s and 1990s, the ISMP, USP, Institute for Healthcare Improvement and The Joint Commission worked to bring attention to the dangers associated with the use of concentrated potassium chloride, which led to changes in the way potassium chloride was packaged, labeled and handled. Despite these changes, serious errors continue to occur with use of these concentrated potassium chloride products.

The SMEs who were interviewed utilized injectable potassium chloride in PN mixtures, IV fluid bags, and occasionally, diasylate fluid. The SMEs shared a preference for commercially available potassium chloride products and did not see a need for products of different concentrations and/or size. One SME suggested that premixed IV bags with potassium chloride might be preferable to compounding in-house due to lower risk of contamination and error, and possibly lower cost, with these products. A few SMEs expressed concern that potassium chloride products with concentrations, sizes and/or packaging different from commercially available products may lead to medication errors. Most of the SMEs had not experienced shortages of potassium chloride, although a few recalled periods when they had been unable to obtain certain vial or bottle sizes.

There were no respondents to the survey distributed via professional medical associations. From the prequestionnaire, 0 respondents reported obtaining potassium chloride 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 potassium chloride to your patients?
    - Yes
    - No
3. Do you prescribe or administer potassium 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 potassium chloride for the following conditions or diseases: (check all that apply)
    - Hypokalemia prevention or treatment
    - Other (please explain) _____
5. I prescribe or administer potassium chloride with my patients as the following: (check all that apply)
    - FDA-approved drug product
    - Compounded drug product
    - Other (please explain) _____
6. I use compounded potassium 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 potassium chloride
    - Other (please explain) _____
7. Do you stock non-patient-specific compounded potassium chloride at your practice?
    - Yes
    - No
    - I'm not sure
8. I obtain compounded potassium 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) _____

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
    - Potassium 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.