Summary Report

Sodium phosphate monobasic anhydrous

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Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
CABG	Coronary artery bypass graft
CPD	Citrate phosphate dextrose
CP2D	Citrate phosphate double dextrose
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HTK	Histidine-tryptophan-ketoglutarate
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of sodium phosphate monobasic anhydrous (sodium phosphate; UNII code: 3980JIH2SW), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

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

REVIEW OF NOMINATION

Sodium phosphate was nominated for inclusion on the 503B Bulks List by Specialty Sterile Pharmaceutical Society (SSPS). Sodium phosphate was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Sodium phosphate was nominated for use as an anticoagulant in cardioplegic solutions via intracardiac injection solution. Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of sodium phosphate.[6,7]

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.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of sodium phosphate products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English

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

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

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing sodium phosphate. 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

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe two concepts: sodium phosphate, citric acid, sodium citrate or dextrose; and surgical cardiac procedures, cardioplegia or intracardiac administration (refer to Appendix 1 for full search strategies). Results were limited to human studies in English language. Searches were conducted on November 5, 2020. In addition, the ECRI Guidelines Trust® repository was searched on November 5, 2020 for clinical practice guidelines that recommended the use of sodium phosphate and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.3.3 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which sodium phosphate was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if sodium phosphate was used as: an FDA-approved product in the nominated dosage form, ROA, or combination; a dosage form, ROA, or combination that was not nominated; or an unspecified dosage form or ROA. Studies in which Buckberg solution was utilized but the formulation for the solution was not provided were excluded. Studies in which sodium phosphate was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or

historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of sodium phosphate ; setting; total number of patients; number of patients who received sodium phosphate ; patient population; indication for use of sodium phosphate ; dosage form and strength; dose; ROA; frequency and duration of therapy; use of sodium phosphate in a combination product; use and formulation of sodium phosphate in a compounded product; use of sodium phosphate compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

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

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

Survey

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

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

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

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

CURRENT AND HISTORIC USE

Results of background information

- Sodium phosphate is not available as an FDA-approved product in the nominated combination. The nominated combination is available as an approved blood product as part of a collection set intended for blood collection. Sodium phosphate monobasic anhydrous is available as an FDA-approved injection in combination with sodium phosphate monobasic anhydrous dibasic heptahydrate. Sodium phosphate monobasic anhydrous is also available as an FDA-approved injectable product in combination with other electrolytes and dextrose.
- Sodium phosphate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for sodium phosphate.
- Sodium phosphate is available in the nominated dosage form and ROA in Canada.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Sodium phosphate monobasic / Citric acid / Sodium citrate / Dextrose	2.22 g/L / 2.99 g/L / 26.3 g/L / 25.5 g/L	Solution	Blood collection	Approved blood product	12/6/1977
Sodium phosphate monobasic / Citric acid / Sodium citrate / Dextrose / Adenine	0.155 g/70 mL / 0.229 g/70 mL / 1.84 g/70 mL / 2.23 g/70 mL / 0.019 g/70 mL	Solution	Blood collection	Approved blood product	5/12/1978

[a]Source: Food and Drug Administration Approved Blood Products Complete List of Currently Approved New Drug Applications (NDA) and Abbreviated New Drug Applications (ANDA) Application Submissions.
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Sodium phosphate monobasic / Citric acid / Sodium citrate / Dextrose	2.51 g/L / 3.27 g/L / 26.3 g/L / 25.5 g/L	Solution	–	Canada	Ethical	8/22/2016
Sodium phosphate monobasic / Citric acid / Sodium citrate / Sodium chloride / Dextrose / Adenine	0.276 g/100 mL / 0.042 g/100 mL / 0.588 g/100 mL / 0.410 g/100 mL / 1.1 g/100 mL / 0.03 g/100 mL	Solution	–	Canada	Ethical	5/31/2013

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

Study selection

Database searches yielded 866 references; 9 additional references were identified from ECRI Guidelines Trust® and included studies from another nominated substance (aspartic acid). After duplicates were removed, 673 titles and abstracts were screened. After screening, the full text of 246 articles were reviewed. Finally, 21 studies were included. Two hundred twenty-five studies were excluded for the following reasons: wrong study design (109 studies); wrong drug (88); unspecified formulation (16); indication not nominated (4); no clinical use (3); unable to obtain full text (2); not in English language (2); duplicate reference (1).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 21 included studies were published between 1984 and 2020. There were 11 experimental studies, 8 observational studies, 2 descriptive studies, and 0 clinical practice guidelines. The 21 studies were conducted in the following countries: Canada, Finland, France, Germany, Iran, Italy, Japan and the US.

A total of 2004 patients participated in the 21 included studies. The number of patients in each study ranged from 14 to 452.

Outcome measures differed among the included studies and included: incidence of perioperative myocardial infarction or arrhythmias; hemodynamic parameters; creatine kinase MB, troponin T and/or endothelin-1 levels; survival and mortality.

Refer to Table 5 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of sodium phosphate

One thousand three hundred and two patients received sodium phosphate as a component of citrate/phosphate/dextrose (CPD) in a cardioplegic solution for induction, maintenance and/or reperfusion in surgical cardiac procedures, such as coronary artery bypass graft (CABG) or valve replacement, requiring cardiopulmonary bypass.[8-26] Twenty-three patients received CPD as part of an enriched solution during reperfusion after lung transplantation.[27] Fourteen patients with coronary heart disease who experienced perioperative cardiac arrest received CPD as part of a cardioplegic solution.[28]

Refer to Tables 6 and 7 for summaries of dosage by indication.

Sodium phosphate was not used as a compounded product, but it was used in a combination product (refer to Tables 8-9).

In 12 studies, the authors' concluding statements were not related to the use of CPD in cardioplegic solutions.[8-11,13,17,18,23-25,27,28] In 6 studies, the authors' concluding statements did not recommend the use of cardioplegic solutions with CPD, or recommended further investigation.[12,15,16,20,22,26] In 3 studies, the authors' concluding statements recommended the use of a cardioplegic solution with CPD.[14,19,21] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 21 included studies, additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of sodium phosphate.

Cardioplegia is defined as "an elective, rapid and reversible paralysis of the heart during cardiac surgery."[29] Cardioplegic solutions are used to intentionally arrest the heart during complex cardiac surgeries.[29] By cross clamping the aorta, transferring systemic circulation to a heart-lung machine and instilling a cardioplegic solution, the surgeon is afforded a motionless and relatively bloodless operating field while myocardial oxygen demand is reduced and the heart is relatively protected from ischemic damage.[29-32]

According to Ali *et al*, cardiopulmonary bypass was first utilized in 1951.[30] A few years later, in 1955, Melrose *et al* published the first description of cardioplegia, using potassium citrate to induce cardiac arrest in dogs.[33] In 1958, Melrose and Gerbode reported the use of potassium citrate in 34 human patients undergoing cardiac surgery.[34] Unfortunately, the high concentration of potassium in the solutions that Melrose and his colleagues used caused dysrhythmias and myocardial necrosis, leading to the death of many patients.[29,35] As a result of these poor outcomes, the use of hyperkalemic solutions fell out of favor for many years. The techniques of pharmacologic arrest were maintained by surgeons in Germany, in particular Hans J. Bretshneider who described the function of each element in cardioplegic solutions and developed a solution now known as histidine-tryptophan-ketoglutarate (HTK).[29,34-36] This solution had a sodium concentration similar to the myocardial intracellular sodium concentration, leading such solutions to be called 'intracellular' cardioplegia.[35] Today, HTK is available in some countries as Custodiol®. In the 1970s, Gerald Buckberg, who "can be credited with stimulating the major shift to the myocardial protective techniques used today", pioneered the use of blood-based cardioplegic solutions.[34] More cardioplegic solutions were formulated in the 1970s and 1980s, including the solutions created at St. Thomas' Hospital in London, one of which is currently available in the US as Plegisol®.[29,35] In 1995, Pedro del Nido introduced del Nido solution, a cardioplegic solution that has been widely used in pediatric patients for many and has recently gained acceptance for use in adult patients.[31,35]

Many of the cardioplegic solutions developed over the past 50 years remain in use today. These solutions differ in their composition, temperature and method of administration.[31] Cardioplegic solutions are either based on a pure crystalloid solution or a mixture of blood and crystalloid.[37] Pure crystalloid solutions, such as St. Thomas solution, are classified as either intracellular or extracellular. Blood-based cardioplegic solutions, such as Buckberg solution, typically contain blood and crystalloid in a 4:1 ratio. Some solutions, such as del Nido, have a blood to crystalloid ratio of 1:4.[37] Microplegia utilizes a minimal amount of crystalloid for a blood to crystalloid ratio of at least 66 to 1.[37] Blood-based cardioplegia theoretically offers several advantages compared to crystalloid cardioplegia, including innate buffering capacity and free radical scavenging; normal oncotic pressure; enhanced oxygen delivery; and rheologic protection for the vasculature.[32,35]

Although the composition of cardioplegic solutions vary, a high concentration of potassium delivered in a crystalloid or blood carrier solution remains a constant.[32,37] 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.[32,37] Cardioplegic solutions contain other

electrolytes and additives to facilitate cardiac arrest and protect the heart during ischemia and reperfusion.

One of the concerns with cross clamping the aorta, cardiopulmonary bypass and cardioplegia is reperfusion injury. Reperfusion injury is defined as the "metabolic, functional and structural consequences of restoring coronary flow" after a period of ischemia.[38] In the cardiovascular system, reperfusion injury is associated with arrhythmias, myocardial dysfunction, decreased cardiac output and vascular damage.[26] Although the precise mechanisms of reperfusion injury in the heart are unknown, calcium and reactive oxygen species are thought to play a major role.[26,39] Calcium is essential to normal functioning of the heart and is involved in the cardiac response to ischemia and reperfusion.[39,40] Munsch explained that "Loss of cell membrane control over calcium influx during postischaemic reperfusion leads to a rise in intracellular calcium, increasing energy utilization and ATP [adenosine triphosphate] consumption, producing contracture or 'stone heart'."[41] The cardiac surgeon, Buckberg observed, "is in the unique position to counteract the potential of reperfusion damage since the conditions of reperfusion and the composition of the reperfusate are under his immediate control."[42] Several modifications have been made to cardioplegic solutions in an attempt to reduce ionized calcium during reperfusion. These modifications include adding CPD, magnesium or calcium channel blockers, such as nifedipine, verapamil and diltiazem, to the solution.[26,39,41] Cardioplegic solutions cannot be completely devoid of calcium or a condition known as the calcium paradox will occur. Calcium is a critical component of the sarcolemma; the absence of calcium in a cardioplegic solution will increase the permeability of the sarcolemma, allowing an influx of calcium when serum calcium corrects with release of the aortic cross-clamp or a calcium-containing solution is administered.[40,43]

CPD and citrate/phosphate/double dextrose (CP2D) are combinations of sodium citrate, sodium phosphate monobasic, citric acid and dextrose that have been used as anticoagulants for whole blood and blood components since the 1950s.[44] CPD is still the preferred anticoagulant in blood products.[44] Dr. Buckberg and colleagues, utilized CPD as a calcium chelator in cardioplegic solutions in a series of experiments in dogs and humans in the 1970s and 1980s.[45-47] CPD remains a component of Buckberg solution today.[12,20,24,26,48,49]

In a 1991 review, Donnelly and Djuric provided the composition of 11 cardioplegic solutions used in hospitals around the US.[43] Five of these solutions, 2 from the New England Medical Center in Boston, Massachusetts and 3 from the University of Illinois Hospital in Chicago, Illinois included CPD. These solutions, all of which were blood-crystalloid combinations, contained 57.3 to 226 mL of CPD. In 2004, Allen published the formula for the warm induction and reperfusate cardioplegic solutions used at the University of Texas at Houston Memorial Hermann Children's Hospital, which included 125 mL of CPD.[8] Several authors have published formulas for Buckberg solution. Kim *et al,* Siddiqi *et al* and Borden *et al* provided nearly identical formulas for Buckberg solution during induction, maintenance and reperfusion.[12,35,48] For induction, the solution had 60 mL of tromethamine, 30 mL of CP2D and 18 mL of potassium chloride (36 mEq) in 392 mL of dextrose 5% in 0.225% normal saline.[12,35] For maintenance, the solution had 123 mL of tromethamine, 61 mL of CP2D and 18 mL of potassium chloride in 798 mL of dextrose 5% in 0.225% normal saline. For reperfusion, the solution had 56 mL of tromethamine, 113 mL of CP2D, 7.5 mL of potassium chloride (15 mEq), 62.5 mL of glutamate/aspartate and 26 mL of dextrose 70% in 235 mL of sterile water. In 2019, Spellman provided the composition of several common cardioplegic solutions, including Buckberg, which 50 mL of tromethamine, 20 mL of CPD and 28 mmol of potassium chloride.[32] The other solutions, including Bretschneider, Custodial®, St. Thomas and Plegisol®, did not contain CPD.

In a 2018 retrospective study from Germany, Kuhn *et al* investigated the effect of cold Buckberg solution versus warm Calafiore solution in patients undergoing coronary artery bypass graft surgery due to acute coronary syndrome.[49] Two hundred seventy-three patients received Buckberg cardioplegia and 677 patients received Calafiore cardioplegia, at the discretion of the operating surgeon. Thirty-day all-cause mortality and overall rates of major adverse cardiac events were comparable between the two groups. Patients who received Buckberg cardioplegia had a higher incidence of stroke and need for prolonged ventilation compared to patients who received Calafiore cardioplegia. After propensity matching, the mortality rate was slightly lower and rate of major adverse cardiac events higher in the Buckberg group compared to the Calafiore group. The incidence of cardiac cause of death was comparable in both groups after propensity matching. The authors concluded that "both intermittent cold and warm blood cardioplegia offer acceptable myocardial protection for patients undergoing urgent or emergency myocardial revascularization due to ACS [acute coronary syndrome]. Both cardioplegic solutions provide safe options to achieve cardiac arrest for CABG [coronary artery bypass graft] procedures."[49] Several other clinical studies were identified in which Buckberg solution was utilized for cardioplegia.[50-61] These studies were not included in the systematic literature review because they did not provide a formulation for Buckberg solutions and therefore, use of CPD could not be confirmed. These studies were published between 1993 and 2019 by investigators from Brazil, Germany, Italy, Poland, the UK, and the US.

The cardioplegic solutions that clinicians choose to use vary from hospital to hospital and around the world. A 2012 survey explored cardioplegic practices in pediatric cardiac surgery amongst members of the Congenital Heart Surgeons' Society.[62] A majority of the 56 respondents used blood-based cardioplegia (48, 86%); only 8 respondents (14%) used crystalloid cardioplegia. The most commonly used solutions were: del Nido (21, 38%); custom-mixed (19, 34%); St. Thomas, Plegisol® or Baxter (9, 16%); Custodiol® (4, 7%) and microplegia (3, 5%). Amongst the respondents who reported using a custom-mixed solution, calcium content was a common target for adjustment, perhaps, the authors suggested, because the immature myocardium has been found to be more sensitive to the calcium concentration of cardioplegic solutions than the mature myocardium. Common additives to the custom-mixed solutions included: magnesium (8, 42%); substrates such as glutamine and aspartate (7, 37%); lidocaine (5, 26%); and insulin (4, 21%). The authors concluded "Myocardial protection techniques still remain highly variable among congenital heart surgeons. This survey demonstrates that there is a perception that del Nido and Custodiol solutions can offer appropriate myocardial protection for longer intervals with decreased repeat dosing."[62]

The Global Cardiopulmonary Bypass Survey, conducted in 2015 with results published in 2017 and 2018, found regional differences in cardioplegic practices.[30,63] The survey was distributed via specialist cardiothoracic anesthesiology societies around the world. A total of 923 responses were analyzed with 334 responses from North America (36%), 269 responses from Europe (29%), 215 responses from South America (24%) and 105 responses from Australia and New Zealand (11%). Blood cardioplegia was the most common type of chemical cardioplegia used in all regions, with the exception of South America where crystalloid cardioplegia was more common.[30] St. Thomas solution was the most commonly used cardioplegic solution in all regions other than North America, where the University of Wisconsin solution was most commonly used (75, 34.9%). The other solutions that respondents from North America reported using included St. Thomas solution (37, 17.2%), other (35, 16.3%), unknown (25, 11.6%), del Nido solution (23, 10.7%), and Bretschneider solution (20. 9.3%). The non-response rate for this question was high, with 58.7% of respondents from North America not responding and 49.8% of respondents overall not responding. The use of additives was common amongst respondents from North America (89, 40.1%) and Australia and New Zealand (33, 40.7%)

and rare amongst respondents from Europe (17, 9.2%) and South American (25, 24%). The most commonly used additives in all regions were glucose, glutamate, aspartate and tromethamine. The authors of this study concluded "The results of this survey have revealed significant regional variation in cardioplegia practices, in terms of the use of blood versus crystalloid cardioplegia, as well as in the type and dilution of cardioplegia solution and the use of additives."[30]

Recently, there has been an interest in exploring the use of del Nido solution, and other single-dose cardioplegic solutions, and microplegia in adult cardiac surgeries. Single-dose cardioplegia reduces or eliminates the need for redosing that is necessary when conventional cardioplegic solutions are used. In a 2019 systematic review and meta-analysis, An *et al* compared the efficacy and safety of del Nido cardioplegia to conventional cardioplegia in adult patients undergoing cardiac surgery.[64] The authors included 13 studies, 7 of which were adjusted observational studies, 5 of which were unadjusted observational studies and 1 of which was a randomized controlled trial, for a total of 1910 patients. There was no difference in 30-day or in-hospital mortality between del Nido cardioplegia and conventional cardioplegia, nor was there a difference in incidence of stroke, atrial fibrillation, acute kidney injury, or intensive care unit or hospital length of stay. Del Nido cardioplegia was associated with a shorter aortic cross-clamp and cardiopulmonary bypass times as well as reduced volume of cardioplegia administered compared to conventional cardioplegia. The authors concluded that "Our findings suggest that DC [del Nido cardioplegia] is safe for use in conventional adult cardiac surgery (CABG [coronary artery bypass graft], valve surgery, and combined CABG/valve surgery) and may potentially offer enhanced myocardial protection with comparable clinical outcomes."[64]

In another 2019 meta-analysis, Gambardella *et al* evaluated the use of single-dose cardioplegia (del Nido or HTK) versus multidose cardioplegia (blood- or crystalloid-based solutions) in adult cardiac surgery patients.[65] Twenty-three studies with a total of 5516 patients were included. There was no difference in either operative mortality or myocardial infarction between patients who received single-dose cardioplegia and those who received multidose cardioplegia. Patients who received del Nido solution had decreased ischemic time, cardiopulmonary bypass time, incidence of reperfusion fibrillation and cardiac enzymes compared to patients who received multidose cardioplegia. These findings were not replicated in patients who received HTK solution; these patients had an increased cardiopulmonary bypass time and incidence of reperfusion fibrillation compared to patients who received multidose cardioplegia. The authors of this study observed that "ultimately surgeons are interested in (1) the best cardiac protection (2) that can be delivered in the least cumbersome fashion, to optimize results and streamline the operative process" and suggested that single-dose cardioplegic solution are ideally suited to fulfill this second point.[65] Based on their findings, the authors concluded that "Compared with multidose cardioplegia, there were advantages in adopting single-dose cardioplegia only in the form of DN [del Nido] solution."[65]

In a study published in 2020, del Nido solution was again compared to conventional cardioplegia, specifically blood cardioplegia, in adult cardiac surgery patients.[66] The authors of this analysis noted that they included all study types whereas previous meta-analyses included mainly retrospective studies or randomized controlled trials and propensity-matched cohorts. Twenty-nine studies were included; the primary outcome measure, mortality, was reported in 26 of these studies for a total of 6679 patients. There was no difference in mortality between patients who were administered del Nido cardioplegia and those who were administered blood cardioplegia. The duration of aortic cross-clamp and cardiopulmonary bypass, as well as cardioplegic volume administered, was less in patients who received del Nido cardioplegia versus those who received blood cardioplegia; however, there was significant heterogeneity for these outcome measures. Significantly fewer patients who received

del Nido solution needed defibrillation for return to spontaneous rhythm after aortic cross-clamp release compared to those who received blood cardioplegia (57 versus 220). Although there was no difference in mortality between the two groups, the authors concluded that del Nido solution is a valuable option in adult cardiac surgeries because "Single dosing of del Nido cardioplegia essentially allows better workflow ergonomics for the surgeon, with fewer interruptions, which may be important in achieving shorter AoX [aortic cross-clamp] and CPB [cardiopulmonary bypass] times, with accrued benefits."[66]

In a series of articles published in the *Journal of Cardiothoracic and Vascular Anesthesia* in 2019, authors argued either for or against more generalized use of del Nido cardioplegia in adult cardiac surgery patients.[32,67] Spellman, who argued for more generalized use of del Nido cardioplegia, observed that many studies had been published in which del Nido cardioplegia was compared to conventional cardioplegia in adults undergoing a variety of surgical cardiac procedures.[32] This author shared that del Nido solution had been used almost exclusively at his institution (Columbia University Medical Center in New York) since 2011. Gorgy and Shore-Lesserson argued against more generalized use of del Nido cardioplegia, pointing out that the currently available studies do not address how often del Nido solution needs to be re-dosed in adult patients nor do they describe the safety of del Nido solution in complex cardiac surgeries of long duration.[67]

Microplegia offers many of the benefits of conventional blood- or crystalloid-based cardioplegia without the risk of volume overload and ensuing hemodilution and myocardial edema that may occur with administration of these solutions.[12] In a 2020 propensity-matched study, the authors noted that a modified Buckberg solution had been used at their institution, the Cleveland Clinic in Cleveland, Ohio, for several decades and microplegia had been introduced in 2012.[12] The authors compared outcomes in 226 propensity-matched pairs of patients who had received microplegia or modified Buckberg cardioplegia while undergoing multicomponent cardiac operations. Patients in both groups had similar in-hospital mortality, incidence of stroke and renal failure, prolonged ventilation, postoperative length of stay and number of transfused blood units. Patients who received microplegia received significantly less crystalloid and had lower peak intraoperative glucose compared to patients who received modified Buckberg solution. The mean cost of cardioplegia per case was significantly less in the microplegia group. The authors explained that the modified Buckberg solution was purchased from a vendor while the crystalloid component for microplegia was made internally, allowing for cost savings. The authors of this study concluded that: "In complex cardiovascular operations with extended aortic clamp times, our simplified microplegia technique significantly reduces the volume of crystalloid administered with cardioplegia, improves perioperative glycemic control, and allows for substantial cost savings relative to Buckberg solution without compromising myocardial protection, morbidity, or mortality."[12]

Cardioplegic solutions are also used for myocardial preservation prior to heart transplantation and for reperfusion once the donor heart has been situated in the recipient. Like patients who undergo cardiopulmonary bypass, transplanted hearts are at risk for ischemia and reperfusion injury. Preservation solutions can mitigate this damage and thereby potentially expand the donor pool and longevity of transplanted organs.[68] Protocols for heart preservation vary both in the type of cardioplegic solution utilized and method of administration (single dose at time of organ procurement or supplemental doses during implantation).[69] In a 1994 survey of 26 hospitals that performed open heart surgery in Missouri, 41 cardioplegic solutions were used, 28 of these solutions were blood-based.[70] Most of the solutions (69% of crystalloid-based and 89% of blood-based) differed substantially from commonly reported cardioplegic solutions. CPD was added to 7 (25%) of the blood-based solutions and glutamate and aspartate were added to 3 (11%) of these solutions. The

authors of this study concluded that limiting the variability of cardioplegic solutions would make it easier to compare outcomes and "It may be desirable to determine the efficacy of custom-made cardioplegia versus that of experimentally proven solutions. Alternatively, a trend toward uniformity may prove more practical."[70] A study published in 1997 found that 167 different preservation solutions were used by 143 active cardiac transplant centers in the US.[71] The most commonly used solutions were custom (54 centers, 42.2%), Plegisol® (29, 22.7%) and Stanford (21, 16.4%). A small number of respondents reporting using CPD as an additive in their solutions at a mean strength of 63.5 ± 7.7 mL/L and range of 54.6 to 68 mL/L.

In a study published in 1993, 62 patients undergoing heart transplantation received either a donor heart preserved with cold St. Thomas solution and uncontrolled reperfusion (group A) or a donor heart preserved with St. Thomas solution with 13 mmol/L aspartate and controlled reperfusion with an aspartate-enriched warm blood cardioplegic solution with CPD.[72] Survival at 1 month and 12 months was similar in both groups. Intraoperative spontaneous defibrillation occurred in 45% (14) of the patients in group B and 0% of the patients in group A. There was a trend towards decreased requirement for inotrope support in group B. The authors revealed that their transplant unit "now employs aspartate-enriched crystalloid cardioplegic arrest, cold storage, and controlled reperfusion with aspartate-enhanced low potassium blood cardioplegia routinely for donor heart preservation."[72] Cannata *et al* evaluated the use of three preservation solutions, HTK-Bretschneider (Custodiol®), Celsior® and St. Thomas (Plegisol®), in adult patients undergoing orthotopic heart transplantation.[73] In-hospital outcomes, specifically death and biventricular failure, did not differ significantly among the three groups of patients, leading the authors to conclude that the type of preservation solution was not a risk factor for these outcome measures.

A 2016 systematic review and meta-analysis evaluated the use of three "more clinically accepted" solutions during cold storage preservation for heart transplant: University of Wisconsin, HTK and Celsior®.[74] Eight studies were included in the systematic review, 6 of these studies were included in the meta-analysis. Four studies compared University of Wisconsin solution to Celsior® in a total of 5301 hearts. Use of University of Wisconsin solution was associated with significantly better survival at 30 and 90 days and 1 year compared to use of Celsior®. Two studies compared University of Wisconsin solution to HTK in a total of 1091 hearts. University of Wisconsin solution was associated with significantly better survival compared to HTK but meta-analysis could not be performed due to differences in outcome measures. Two studies compared HTK to Celsior® in a total of 147 hearts. No significant differences in either heart dysfunction or in-hospital mortality were detected between these two solutions. The authors of this study concluded that their findings "suggests that University of Wisconsin solution has superior clinical outcomes for heart transplantation during cold static storage preservation compared with the other solutions, and Celsior solution has similarly protective effects compared with histidine–tryptophan– ketoglutarate solution in donor heart preservation."[74] Recently, Mohr *et al* described a novel preservation solution, HTK-N, in which glycine, alanine and arginine were added to the solution, N-acetyl-histidine partially replaced histidine, and aspartate and lactobionate substituted for chloride.[68] This solution has been tested in several in several animal models of solid organ transplantation; results from its use in human patients have yet to be published.

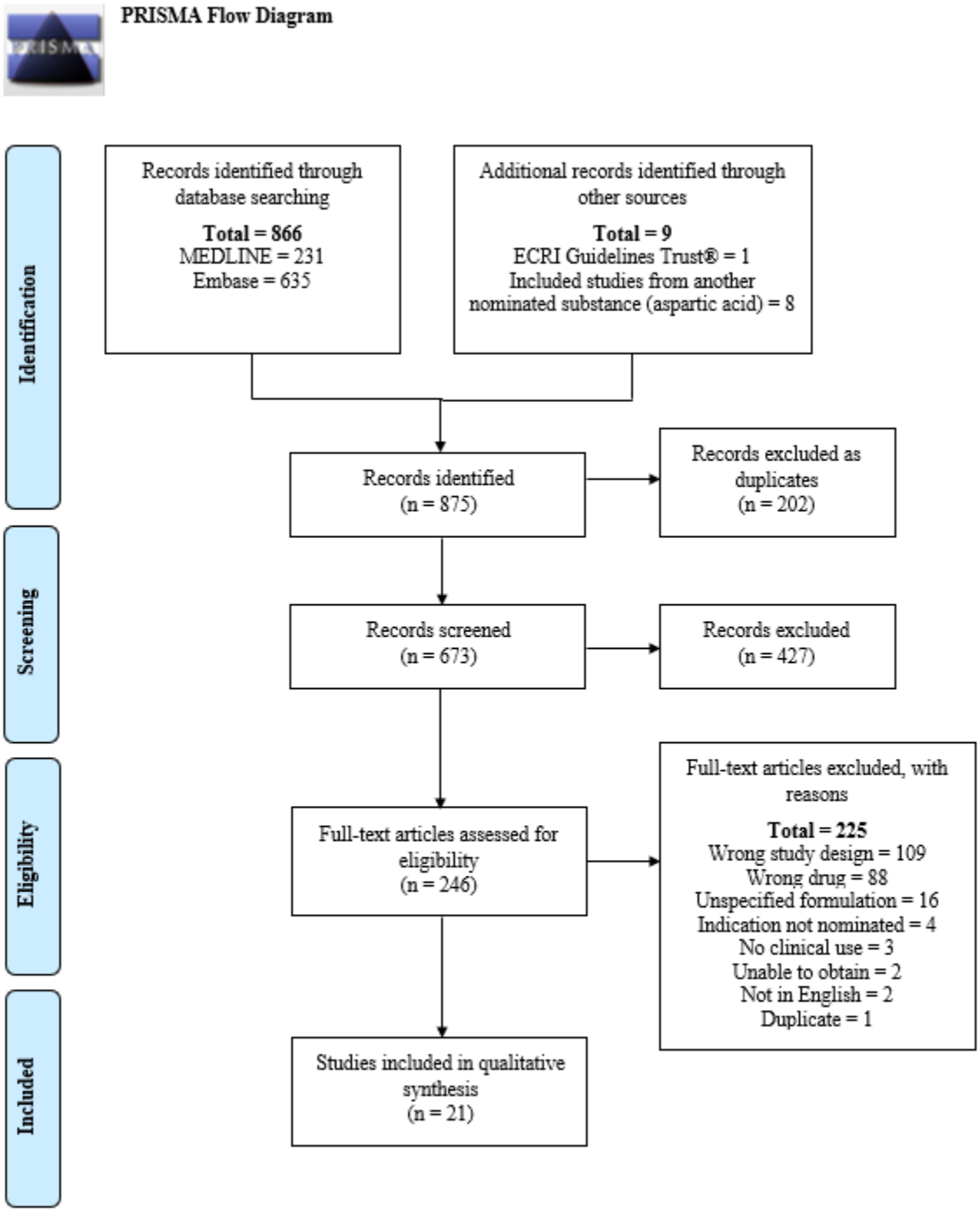
The ideal composition of cardioplegic solutions has been debated since Melrose *et al* first described the use of potassium citrate to induce cardiac arrest in dogs in 1955.[33] Understanding the complexities of maintaining arrest and limiting the consequences of prolonged ischemia and reperfusion continues to evolve, as do the surgical procedures for which cardioplegia is used. It is difficult to compare the safety and efficacy of cardioplegic solutions given the variability of the

solutions themselves, how they are administered, and the patients to whom they are administered. In an article published in 1998, Arsenian commented that "While studies showing protective effects of glutamate and aspartate in cardioplegia have been cited, it must be acknowledged that there is no consensus on the ingredients of a cardioplegia solution."[75] In 2001, Dr. Buckberg shared two incidents that demonstrate the need for evaluation of ingredients in cardioplegic solutions, safe manufacturing and storage of cardioplegic solutions, and clinicians and staff who know how to administer these solutions.[36] In the first incident, a surgeon using Buckberg cardioplegic solution (with high potassium and CPD) did not dilute the solution 4:1 prior to administration and a patient died. In the second incident, a change in manufacturing practices at a hospital pharmacy led to *Escherichia coli* contamination of a few bottles of cardioplegic solution. Not all of the remaining bottles were checked or discarded; the use of these bottles led to the death of 2 patients and serious infection in 6 patients. This incident led Buckberg to ask a commercial pharmacy to produce the cardioplegic solution utilized at his hospital so others would not have to make the solution at their own hospital pharmacies. Buckberg cautioned that "Similar problems with either improper additives or bacterial contamination can occur when perfusionists, with no pharmacologic or electrolyte physiologic background, must construct a cardioplegic solution. This may be especially problematic if performed under emergency circumstances" and adverse effects may arise from changing cardioplegic solutions without adequate clinical testing.[36] Spellman echoed this opinion in 2019, writing that "Rather than placing focus on the need to study specific individual formulations, a firm understanding of the benefits of the specific components of a cardioplegia solution…along with safe pharmacy manufacturing, should guide the selection of an optimal solution for myocardial preservation in cardiac surgical patients."[32]

In the US, there are currently two FDA-approved products for cardioplegia/cardiac perfusion: Plegisol® made by Pfizer and a generic equivalent made by Baxter. These solutions are a combination of: calcium chloride, which is present to maintain the integrity of the cell membrane and thereby avoid the calcium paradox during reperfusion; magnesium chloride, which helps stabilize the myocardial membrane and protect adenosine triphosphate (ATP) reserves; potassium chloride to induce cardiac arrest; and sodium chloride, which helps preserve the ionic integrity of the myocardium and maintain an electroneutral solution.[76] Sodium bicarbonate is added to this solution to adjust the pH prior to administration.

Cardioplegic solutions are on the Institute of Safe Medication Practices (ISMP) list of high-alert medications in acute care settings.[77] 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.

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3.Types of studies

Types of Studies	**Number of Studies**
Descriptive[10,28]	2
Experimental[14-19,21,22,24-26]	11
Observational[8,9,11-13,20,23,27]	8

Table 4. Number of studies by country

Country	**Number of Studies**
Canada[14]	1
Finland[17,18,25]	3
France[21]	1
Iran[26]	1
Italy[19]	2
Japan[15,16]	2
United States (US)[8,9,11-13,20,23,24,27]	9
Multiple Countries • Germany, US[10,28]	2
	Total US[a]: 11 Total Non-US Countries[a]: 12

[a]Studies 10 and 28 counted in both US and non-US total.

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Surgical cardiac procedures requiring cardiopulmonary bypass					
Allen *et al.*, 1986, US[9]	Retrospective	31 Patients with acute coronary occlusion • Medical streptokinase (sex not provided, mean 56 y ± 4) • Medical angioplasty (not provided, mean 57 y ± 3) • Surgical (sex not provided, mean 56 y ± 3)	Reperfusion established via: • Medical streptokinase: intracoronary streptokinase alone (11) • Medical angioplasty: angioplasty ± intracoronary streptokinase (10) • Surgical: coronary artery bypass graft (CABG) (10)	Hemodynamic instability, reperfusion arrhythmias, myocardial infarction, creatine kinase, global and regional contractility	"These studies imply that acute coronary occlusion is treated best by control of the conditions of reperfusion and the composition of the reperfusate."
Allen, 2004, US[8]	Retrospective	93 Children undergoing a Norwood procedure (sex not provided, mean 7 days, range 2-44 days)	• Warm induction and reperfusion with blood cardioplegic solution with citrate/phosphate/dextrose (CPD) and aspartate/glutamate (not mentioned) • Cold induction and multidose blood cardioplegic solution with CPD (not mentioned) • Modified cold blood maintenance solution with CPD (not mentioned)	Overall survival; fractional shortening on echocardiogram; ejection fraction on angiogram	"These studies provide direct evidence that excellent protection of the stressed pediatric heart is possible by using a cardioplegic protection strategy."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Beyersdorf and Buckberg, 1992, Germany, US[10]	–	74 Patients with acute coronary occlusion who underwent emergency surgical revascularization (sex, age not provided) 112 Patients with myocardial infarction who underwent emergency coronary revascularization (sex, age not provided)	Controlled regional reperfusion with blood cardioplegic solution (186)	Regional contractility	"These clinical results, together with our recent reports, provide confirmation of our belief that the fate of jeopardized myocardium is determined by how the reperfusion strategy is managed, rather than by how quickly the blood supply is restored."
Bhaya *et al*., 2015, US[11]	Prospective	22 Patients who underwent on-pump cardiac surgery (68%, mean 50.9 y, range 27-80 y)	• Intermittent antegrade infusion of cold blood cardioplegia (12) • Intermittent antegrade infusion of cold blood cardioplegia and retrograde cardioplegia with warm aspartate/glutamate-enriched solution (10)	Left ventricular free wall and interventricular septal function by 2-dimesnional transthoracic echocardiography and 3-dimensional transthoracic speckle tracking echocardiography	"The integrated blood cardioplegia method, which combines cold antegrade/retrograde delivery and warm reperfusion, offered superior myocardial protection during surgery when compared with cold antegrade blood cardioplegia..."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Borden *et al.*, 2020, US[12]	–	452 Patients who underwent multicomponent operations • Microplegia (67%, mean 61 y ± 14) • Buckberg (63%, mean 62 y ± 13)	• Microplegia (226) • Buckberg cardioplegia (226)	Postoperative troponin T; need for postoperative circulatory support; new ventricular dysfunction or wall motion abnormality; volume of crystalloid infused with cardioplegia; lowest intraoperative hematocrit; number of red blood cell units transfused	"In complex cardiovascular operations with extended aortic clamp times, our simplified microplegia technique significantly reduces the volume of crystalloid administered with cardioplegia, improves perioperative glycemic control, and allows for substantial cost savings relative to Buckberg solution without compromising myocardial protection, morbidity, or mortality."
Bottner *et al.*, 1991, US[13]	–	64 Patients undergoing emergency bypass grafting for failed angioplasty • Group 1 (69%, mean 58.2 y ± 7.5) • Group 2 (74%, mean 58.8 y ± 10)	All cardioplegic solutions had CPD • Group 1: Patients treated prior to February 1987, received cold induction and maintenance cardioplegia, no reperfusion cardioplegic solution (45) • Group 2: Patients treated after February 1987, received normothermic induction cardioplegia, cold maintenance cardioplegia and normothermic reperfusion cardioplegia (19)	Myocardial infarction	"The marked reduction in perioperative myocardial infarction as assessed by enzyme and electrocardiographic evaluation suggests a 'salvage' effect for the normothermic cardioplegia strategy for ischemic myocardium in the setting of failed angioplasty."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Fremes *et al.*, 1984, Canada[14]	Prospective, randomized trial	90 Patients undergoing elective CABG • Blood cardioplegia (88%, mean 55.2 y ± 8.9) • Crystalloid cardioplegia (89%, mean 56.2 y ± 8.5)	Patients randomized to receive: • Blood cardioplegia with CPD (43) • Crystalloid cardioplegia with no CPD (47)	Perioperative myocardial infarction, creatine kinase-myocardial band	"BCP [blood cardioplegia] provides superior protection for elective coronary bypass grafting and may improve the clinical results in patients with unstable angina or in other high risk patients."
Hayashi *et al*., 2004, Japan[16]	–	70 Patients who underwent elective CABG (78.6%, mean 67.6 y 7.5)	Patients randomized to: • Group M: Minimally diluted blood cardioplegia supplemented with potassium chloride and magnesium sulfate (35) • Group C: Standard 4:1 blood-crystalloid cardioplegia with Buckberg solution containing CPD (35)	Time required to achieve cardioplegic arrest; incidence of spontaneous heartbeat recovery after aortic unclamping; postoperative atrial fibrillation; total amount of crystalloid solution administered; maximum dose of dopamine required after termination of cardiopulmonary bypass; creatine kinase-myocardial band	"Although the present study has methodical limitations and there remain several issues to be examined, 'initial, continuous and intermittent bolus' administration of minimally-diluted BCP [blood cardioplegia] supplemented with potassium and magnesium could be a reliable and effective technique for intraoperative myocardial protection."
Hayashi *et al*., 2006, Japan	–	30 Patients with hypertrophied hearts who underwent aortic valve replacement • Group M (60%, mean 71.5 y ± 6.3) • Group C (53.3%, mean 66.9 y ± 8.6)	Patients randomized to: • Group M: Minimally diluted blood cardioplegia supplemented with potassium chloride and magnesium sulfate (15) • Group C: Standard 4:1 blood-crystalloid cardioplegia with Buckberg solution containing CPD (15)	Ventricular fibrillation/tachycardia after aortic unclamping; atrial fibrillation; total amount of crystalloid solution administered; maximum dose of dopamine required; creatine kinase-myocardial band	"In summary, we applied a combination of 'initial, continuous and intermittent bolus' BCP [blood cardioplegia] administration for the management of hypertrophied hearts. This method of cardioplegia administration achieved stable maintenance of cardioplegic arrest, and the use of minimally diluted BCP provided superior myocardial protective effects in comparison with that of standard 4:1-diluted BCP."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Kaukoranta *et al.*, 1995, Finland[17]	Prospective, randomized	101 Patients who underwent CABG • Normothermic (warm) cardioplegia (82%, mean 58.6 y ± 1.3) • Mild hypothermic cardioplegia (80%, mean 58.6 y ± 1.3)	Patients randomized to receive aspartate/glutamate-enriched cardioplegic solution: • Normothermic (51) • Mild hypothermic (50)	Hemodynamics; creatine kinase-MB; complications; 30-day mortality	"In conclusion, we have shown in this prospective, randomized study that both normothermic (37°C) and mild hypothermic (28° to 29°C) retrograde blood cardioplegias, when delivered in near continuous fashion, offer safe myocardial protection during coronary artery bypass grafting performed on patients with severe coronary artery disease."
Kaukoranta *et al.*, 1998, Finland[18]	Prospective, randomized	20 Patients who underwent CABG • Antegrade cardioplegia (60%, mean 63.8 y ± 7.5) • Retrograde cardioplegia (70%, mean 62.3 y ± 8.9)	Patients randomized to receive mild hypothermic aspartate/glutamate-enriched cardioplegic solution: • Antegrade (10) • Retrograde (10)	Adenosine triphosphate on myocardial biopsy; hemodynamics; troponin T; creatine kinase-MB	"Retrograde mild hypothermic blood cardioplegia leads to metabolic changes compatible with right ventricular ischemia. Nevertheless, tissue levels of high-energy phosphates are well preserved, and the postoperative course seems to be unproblematic."
Lanfranconi *et al.*, 1992, Italy[19]	Randomized	100 Patients who underwent CABG • Cold blood cardioplegia, warm substrate-enriched reperfusion (88%, mean 57 y ± 9) • Cold crystalloid cardioplegia (86%, mean 60 y ± 10)	• Cold blood cardioplegia and warm aspartate/glutamate-enriched reperfusion (49) • Cold hyperkalemic crystalloid cardioplegia (51)	In-hospital mortality; perioperative myocardial infarction; weaning time form cardiopulmonary bypass; length of stay in intensive care unit	"In conclusion, in our study, we assessed by simple means that Blood Cardioplegia plus Warm Substrates Enriched Reperfusion provides better myocardial protection in patients undergoing myocardial revascularization."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Mick *et al.*, 2015, US[20]	–	390 Patients undergoing valve surgery • Aortic valve, Buckberg cardioplegia (71.7%, mean 68 y ± 15) • Aortic valve, del Nido cardioplegia (69.4%, mean 69 y ± 14) • Mitral valve, Buckberg cardioplegia (63.6%, mean 56 y ± 12) • Mitral valve, del Nido cardioplegia (71%, mean 56 y ± 12)	Patients who underwent valvular surgery in which del Nido cardioplegia was used were propensity matched with patients who received Buckberg cardioplegia • Aortic valve surgery, Buckberg cardioplegia (85) • Aortic valve surgery, del Nido cardioplegia (85) • Mitral valve surgery, Buckberg cardioplegia (110) • Mitral valve surgery, del Nido cardioplegia (110)	Postoperative troponin T	"del Nido solution can be used safely and effectively as an alternative to Buckberg solution in adult isolated valve surgery and is associated with lower insulin requirements and potential time and cost savings."
Obadia *et al.*, 1996, France[21]	–	28 Patients who underwent coronary revascularization with cardiopulmonary bypass • Crystalloid cardioplegia (100%, mean 65 y ± 8) • Buckberg (blood) cardioplegia (100%, mean 60 y ± 10)	Patients randomized to receive: • Crystalloid cardioplegia with St. Thomas no. 2 solution (14) • Blood cardioplegia with Buckberg solution (14)	Hemodynamic parameters; reperfusion arrhythmias; creatine phosphokinase myocardial band; nucleotide adenine metabolites	"This study of the reperfusion period suggests that cold blood cardioplegia offers a better protection to myocardial energy metabolism by reducing the release of metabolites, purine bases and oxypurine bases into the coronary sinus."
Onorati *et al.*, 2013, Italy[22]	Randomized	80 Patients with unstable angina undergoing CABG • Substrate-enriched microplegia (65%, mean 65.1 y) • Buckberg cardioplegia (55%, mean 66.1 y)	Patients randomized to receive: • Substrate-enriched microplegia (40) • Standard Buckberg solution with CPD (40)	Perioperative troponin I	"In conclusion myocardial protection with microplegia in patients with unstable angina significantly reduced the perioperative myocardial damage and improved the postoperative hemodynamic status, the peripheral perfusion, and the resulting LV [left ventricular] systolic and diastolic function."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Sharma *et al*., 1999, US[23]	–	21 Patients undergoing CABG • Non-diabetic patients (72.7%, mean 62 y ± 3) • Diabetic patients (77.8%, mean 57 y ± 4)	All patients received blood cardioplegic solution with CPD for induction, maintenance and reperfusion	Endothelin-1, nitrite and nitrate	"Reperfusion after CPL [cardioplegia] during coronary artery bypass grafting procedure can trigger the release of endothelin-1 in patients with diabetes mellitus. This may favor increased vascular tone or positive inotropic responses after coronary artery bypass grafting and may contribute to significant cardiovascular consequences in diabetic patients."
Wallace *et al*., 2000, US[24]	Prospective, randomized clinical trial with blinded analysis	62 Patients who underwent CABG • Substrate-enriched cardioplegia (84%, mean 63.2 y ± 9.7) • Cold blood cardioplegia (83%, mean 61.8 y ± 9.7)	All solutions for both groups had CPD: • Induction and reperfusion with warm aspartate/glutamate-enriched cardioplegia + maintenance with cold cardioplegia (32) • Induction and maintenance with cold cardioplegia, no reperfusion (30)	Hemodynamic parameters, creatine kinase-MB	"Our results demonstrate a transient improvement in LV [left ventricular] systolic function in the immediate post-bypass period in CABG patients in the IRWSE [induction and reperfusion with warm substrate-enriched blood cardioplegia] + CB [cold blood] group. The intraoperative benefits of the IRWSE + CB technique did not persist in the postoperative period."
Wistbacka *et al*., 1995, Finland[25]	Prospective, randomized, double-blind clinical study	44 Patients with unstable angina and/or left ventricular ejection fraction < 50% who underwent CABG • Amino acid-enriched solution (91%, mean 62.2 y ± 9.1) • Control (73%, mean 62.5 y ± 8.7)	All patients received aspartate/glutamate-enriched cardioplegic solution; randomized to receive perioperative intravenous infusion of solution with: • Glucose, aspartate, glutamate, insulin, potassium, magnesium, and phosphate (22) • Glucose, potassium, magnesium, phosphate (22)	Hemodynamic parameters, creatine kinase-MB	"Amino acid-enriched GIK [glucose-insulin-potassium] infusion improves hemodynamic function in CABG patients with unstable angina and/or compromised left ventricular function."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Yaghoubi *et al*., 2011, Iran[26]	Double-blind clinical trial	50 Patients undergoing CABG (60%, mean 62.3 y ± 9.1)	At the end of surgery, prior to the opening of aortic cross-clamp, patients randomized to receive: • Warm blood with CPD (25) • Blood only (25)	Left ventricular ejection fraction; serum malondialdehyde; total antioxidant capacity; superoxide dimutase	"According to the results of this study, a solution of CPD is effective in improving the antioxidant status, but has little effect in reducing other markers of oxidative stress. It seems that the reduction of other cations may have a major role in reducing the beneficial effects of this drug that is needed more studies in the future."
Indication 2: Lung transplantation					
Ardehali *et al.*, 2003, US[27]	–	56 Patients who underwent lung transplantation (sex, age not provided)	• Modified reperfusion protocol that removed leukocytes from recipient blood and then administered with a solution that provides aspartate, glutamate and dextrose (23) • Whole blood reperfusion (control, 23)	Incidence of ischemia-reperfusion injury	"This study suggests that modification of the reperfusate content decreases the incidence of ischemia-reperfusion injury in human lung transplantation when compared with whole blood reperfusion in a historical group of patients."
Indication 3: Perioperative cardiac arrest					
Beyersdorf *et al.*, 1992, Germany, US[28]	–	14 Patients with coronary heart disease who had perioperative cardiac arrest (86%, mean 66 y ± 2)	Warm aspartate/glutamate-enriched blood cardioplegic solution (14)	Global and regional wall motion, arrhythmias, creatine kinase, need for pharmacologic or mechanical circulatory support, mortality	"We conclude that witnessed perioperative arrest with intractable ventricular fibrillation should be treated aggressively by administering cardiopulmonary resuscitation during prompt transfer to the operating room for total vented bypass and delivery of warm substrate-enriched blood cardioplegic solution."

Abbreviations: "–", not mentioned; CABG, coronary artery bypass graft; CPD, citrate/phosphate/dextrose.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Amount of Citrate/Phosphate/Dextrose Added to Cardioplegic Solution	Volume of Cardioplegic Solution Administered[a]	Dosage Form	Route of Administration	Duration of Treatment
Induction of cardiopulmonary bypass[8-13,20,23,24]	50 or 225 mL	150-350 mL/minute for 2-5 minutes	Solution	Aorta, coronary sinus	Once
	30 mL[b]	500-700 mL			
	–				
Maintenance of cardiopulmonary bypass[8-13,20,23,24]	50 or 225 mL	200 mL/minute for 2 minutes following completion of each distal anastomosis	Solution	Aorta, coronary sinus, vein graft	Duration of procedure, while aorta cross-clamped
		100-500 mL, every 15-20 minutes and/or on completion of each distal anastomosis			
	61 mL[b]	400 mL every 15-20 minutes		–	
Reperfusion during cardiopulmonary bypass[8-13,20,23,24]	225 mL	150 mL/minute for 2 minutes, then 50 mL/minute for 18 minutes	Solution	Aorta, coronary sinus, graft	Once
		150 mL/minute for 2 minutes, then additional 200 mL			
		450 mL, then 50 mL/minute for each vein graft			
	113 mL[b]	300-400 mL			
Reperfusion during lung transplantation[27]	225 mL	200-500 mL/minute for 3 minutes	Solution	Pulmonary artery	Once
Perioperative cardiac arrest[28]	225 mL	Induction: 250-350 mL/minute for 11 minutes Reperfusion: 150-250 mL/minute for 20 minutes	Solution	Aorta, coronary sinus, graft	Once

Abbreviation: "–", not mentioned.

[b]Amount of citrate/phosphate/double dextrose (CP2D) in cardioplegic solution.

Table 7. Dosage by indication – non-US countries

Indication	Amount of Citrate/Phosphate/Dextrose Added to Cardioplegic Solution	Volume of Cardioplegic Solution Administered[a]	Dosage Form	Route of Administration	Duration of Treatment
Induction of cardiopulmonary bypass[14-18,21,22,25]	20 mL/L	200-300 mL/minute for 2-5 minutes	Solution	Aorta, coronary sinus	Once
	20 mL/302 mL				
	30 mL/700 mL				
	125 mL				
	50 mL	160 mL/m^2		–	
		700 mL		Aorta	
Maintenance of cardiopulmonary bypass[14-18,21,22,25]	20 mL/L	100 mL after completion of each distal anastomosis, 400 mL after completion of each proximal anastomosis	Solution	Aorta, vein graft	Duration of procedure, while aorta cross-clamped
	20 mL/302 mL	200 mL/min for 2 minutes every 30 minutes and continuous at 100 mL/minute, then 80 mL/minute, finally 60 mL/minute		Aorta, vein graft	
	30 mL/700 mL				
	125 mL	200 mL/minute		Aorta, coronary sinus	
	50 mL	300 mL, every 20 minutes		Aorta	
		120 mL/m^2 for 2 minutes, every 20 minutes		–	
Reperfusion during cardiopulmonary bypass[17-19,21,22,25,26]	–	150 mL/minute for 3 minutes	Solution	–	Once
		100 mL/minute/m^2 for 3 minutes			
	225 mL	150 mL/m^2 for 3 minutes			

	113 mL	450 mL		Aorta	
	125 mL	–		Aorta, coronary sinus	

Abbreviation: "–", not mentioned.

Table 8. Number of studies by combination

	Combination Formula	**Number of Studies**
Nominated	Sodium phosphate 0.222% / Citric acid 0.299% / Sodium citrate 2.63 % / D-glucose 2.55% – solution	0
Others found in literature	Sodium phosphate 222 mg / Citric acid 300 mg / Sodium citrate 2.63 g / Dextrose 1.28 g – solution[13]	1
	Sodium phosphate 1.2 mmol/L / Citric acid 1.13 mmol/L / Sodium citrate 6.75 mmol/L / Glucose 18.1 g/L – solution[15,16]	2[a]
	Sodium phosphate 0.78 mmol/L / Citric acid 0.73 mmol/L / Sodium citrate 4.37 mmol/L / Glucose 18.9 g/L – solution[15,16]	2[a]
	Sodium phosphate 0.11 g/L / Citric acid 0.15 g/L / Sodium citrate 1.32 g/L / Dextrose 1.28 g/L – solution[23]	1[a]
	Sodium phosphate 0.25 g/L / Citric acid 0.34 g/L / Sodium citrate 3.0 g/L / Dextrose 18.91 g/L – solution[23]	1[a]
	Sodium phosphate / Citric acid / Sodium citrate / Dextrose[b] – solution[8-12,14,17-22,24-28]	17

[a]Studies 15, 16 and 23 utilized 2 solutions with different concentrations.
[b]Concentrations not mentioned.

Table 9. Compounded products – US

No compounded products from included studies

Table 10. Compounded products – non-US countries

No compounded products from included studies

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. Two SMEs discussed cardioplegia solutions. Both SMEs discussed cardioplegia solutions during interviews conducted in project year 2. The two SMEs were medical doctors. The SMEs specialized and/or were board-certified in cardiothoracic and general surgery, working in academic medical practice. The SMEs had been in practice for 13 to 16 years.

Cardioplegia is used during cardiac surgery in order to arrest the heart while keeping heart cells viable by allowing the Krebs cycle to continue.

In the US, blood-based cardioplegia is used with electrolytes and other components to balance the pH of the solution. The blood carries oxygen to tissues while nitric oxide vasodilates. One SME discussed 3 types of cardioplegic solutions: Buckberg, a dextrose-based solution with tromethamine, citrate-phosphate-2-dextrose and potassium chloride; del Nido, a calcium-free, potassium-rich, non-glucose-based solution; and a commercially available product from Baxter. All are hyperkalemic with differences in additives, such as buffering agents or lidocaine, and the ratio of blood to crystalloid component.

One SME said the most commonly used cardioplegic solutions are Buckberg or St. Thomas. These are given every 15-30 minutes with the goal of keeping the heart perfused. The downside is that you have to administer these solutions frequently, through the coronary arteries. Retrograde cardioplegia can also be used in which the solution is administered via the coronary sinus that flows through the venous system.

The del Nido solution, on the other hand, only needs to be given about every hour, which can make operations more straightforward. It is typically used for minimally invasive, uncomplicated cases in patients with good heart function. The SME said the solution is usually formulated by pharmacists. It was originally used in children, and studies say it can be given every 3 hours for children.

Another cardioplegia solution is the histidine-tryptophan-ketoglutarate (HTK) solution, which is similar to the del Nido solution, but the SME thought it was all electrolytes; the SME had never used this solution but stated that it was used in Europe.

When choosing solutions for cardioplegia, high risk patients (heart failure, poor myocardial function) and more complicated patients will likely receive conventional cardioplegia as repeated doses (Buckberg and St. Thomas). One SME stated that most surgeons use what they were trained with; the choice of cardioplegic solution is an important decision because you need to adequately protect the heart, which can fail if not protected.

One SME only used the commercially available preparation that does not contain citric acid. The SMEs theorized that citric acid might be used more as an anticoagulant; this SME administered heparin before cardioplegia, so no additional anticoagulants were needed because heparinized blood cycles throughout the heart.

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

While a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtain varied from less than 1% to the majority of compounded products used at one participant's facility. A participant stated "we have this method that we use where if we can buy it commercially ready to administer, we do that. If we can't buy it in that format, then we buy it in a vial, for

example, that can be snapped into a Mini-Bag Plus, because we're a Baxter house, as a second preference. If we can't buy it in either of those two formats and we can get it from a 503B, then we do that. And our last resort is compounding internally." Two participants commented that they will not outsource a product unless 2 outsourcing facilities that they contract with are able to compound the product. This redundancy will allow for a quick flip to the other outsourcing facility if there is an issue with a product compounded from one outsourcing facility, minimizing the impact to the participant's facility.

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

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

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

keep up with what the demand is." One participant also commented that they will obtain labor intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The COVID-19 pandemic has also impacted the operations of hospitals with one participant who stated that "it's just really high volume, and the bigger the hospital, the higher the volume, especially when you have one disease state in half of your hospital" and another who expressed that "without 503B, we would've been in significant trouble." One participant commented that "even though the number might be small [percent of products obtained from outsourcing facilities], some of the reasoning is quite critical, and the amount of time that it saves is very significant for beyond what we're able to do and when." Additionally, challenges with recruiting and retaining pharmacy technicians impact decision-making with one participant stating "it is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready to use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing."

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

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

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products utilized. However, the products utilized in a facility are often developed in-house over decades based on physician and nurse requests, and more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, "these practices had evolved somewhat disparately, even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines." This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said "I think we made nine different epidural concentrations, all driven by anesthesia, and they want what they want and 503Bs may not offer that. No one else in the country is buying that same concentration a 503B isn't going to go through the expense of adding that to their product list." The participant continued that "similar with the ADCs [automated dispensing cabinets], we've run into situations where dextrose 50%

goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, 'no, we can't have it, and that's too big it won't fit,' we want it in this format and then we're stuck again because there's no 503B offering a format during that shortage that fits where it needs to go. Then we're stuck in sourcing." Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that "3% saline for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We're either going to draw that out or we're sending it to the ER with stickers all over it saying only give 150 [mL]." The participant continued that "it would be great if the FDA could look at the size of the container that they're approving and whether that's a realistic dose, is it a unit dose or isn't it."

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

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

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

house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products but when they reviewed the facilities, they did not pass their internal quality standards; one facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams due to the potential cross reactivity in patients with allergies. One participant stated that there are some cephalosporins they would like to obtain from an outsourcing facility but cannot because "they would have to build a separate clean room with a dedicated HVAC [heating, ventilation, and air conditioning], so you're talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn't there." Another participant stated that the concentrations required for ophthalmic antibiotics are not available but the labor and risk of compounding these products in-house is not worth it.

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

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

purchased from an outsourcing facility but "more times than not, they go unused and expire." Another stated that they do not keep it in stock because there is a minimum purchase and there are only a few cases a year for whom they need to use alum. The participant had it STAT shipped when needed. Another participant stated that "we had a meeting with the head of urology who was baffled, why they're even ordering it. He was like, 'this is an old, really old. I don't even know why we're using it' and basically approved for us to not even make it anymore for now."

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

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

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

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

The participants also discussed challenges with utilizing outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because "it just hasn't been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to... It just isn't worth the dating that they gave us or can give us." Another commented that they obtain very little product from outsourcing facilities due to the "the amount of work for vetting and continually validating quality of these 503B outsourcing facilities." The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another

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

Results of survey

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

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

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

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

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

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

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which sodium phosphate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded sodium phosphate

No respondents to survey distributed via professional medical associations

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

No respondents to survey distributed via professional medical associations

Table 15. Demographics of prequestionnaire respondents' facilities

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

Urban hospital	5
Number of Beds	**Responses, n (N=38)**
< 50	4
50-99	3
100-199	1
200-299	3
300-399	5
400-599	3
> 600	18

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

Table 16. Reasons for obtaining products from outsourcing facilities

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

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

Table 18. Products obtained from an outsourcing facility

Product	Responses, n (N=108)[a]
Acetylcysteine	1
Adenosine	2
Aluminum potassium sulfate	2
Aspartic acid	0
Atenolol	0
Atropine	9
Baclofen	4
Betamethasone	0

Biotin	0
Bupivacaine	8
Calcium chloride	1
Caffeine sodium benzoate	0
Cholecalciferol	1
Chromium chloride	0
Clonidine	0
Dexamethasone sodium phosphate	0
Diclofenac	0
Gentamicin	0
Glycerin	1
Hydroxyzine	0
Ketamine	14
Levocarnitine	0
Lidocaine	8
Lorazepam	2
Magnesium sulfate	4
Manganese chloride	0
Methylprednisolone	0
Midazolam	15
Mupirocin	1
Norepinephrine	15
Ondansetron	0
Phytonadione	0
Potassium chloride	0
Potassium phosphate	0

Prilocaine	0
Proline	0
Propranolol	1
Ropivacaine	6
Sodium chloride	0
Sodium citrate	3
Sodium phosphate	0
Tetracaine	2
Triamcinolone acetonide	0
Tropicamide	0
None of the above	8

[a]Respondents were allowed to select multiple products.

CONCLUSION

Sodium phosphate was nominated for inclusion on the 503B Bulks List for use as an anticoagulant in cardioplegic solutions via intracardiac injection solution. Sodium phosphate is not available as an FDA-approved product in the nominated combination but is available as an approved blood product as part of a collection set intended for blood collection in the US. Sodium phosphate is also available in the nominated combination in Canada.

From the literature review, several studies were found in which CPD was used as a cardioplegic solution for induction, maintenance and/or reperfusion in surgical cardiac procedures requiring cardiopulmonary bypass. However, in most studies the authors' conclusion was not related to the use of CPD, the authors did not recommend the use of cardioplegic solutions with CPD, or recommended further investigation. Neither SMEs utilized CPD as a cardioplegic solution.

Zero people responded to the survey distributed via professional medical associations and available on the project website. From the prequestionnaire, 0 respondents obtained sodium phosphate from 503B outsourcing facilities.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to November 3, 2020
- Date last searched: November 5, 2020
- Limits: Humans (search hedge); English language
- Number of results: 231
- Note: Did not include 'glucose' as MeSH term because retrieved too many irrelevant results

1	((sodium$ or monosodium$ or disodium$ or trisodium$ or natri$) adj2 (phosphat$ or biphosphat$)).tw.	7407
2	sodiumphosphat$.tw.	4
3	sodium citrate/	759
4	((sodium$ or monosodium$ or disodium$ or trisodium$ or natri$) adj2 citr$).tw.	4161
5	citric acid/	10762
6	(citric$ adj2 acid$).tw.	13284
7	citronensaure.tw.	0
8	dextroglucose.tw.	3
9	dextro glucose.tw.	0
10	dglucose.tw.	21
11	d glucose.tw.	20927
12	dextrose.tw.	12431
13	buckberg.tw.	63
14	or/1-13	63815
15	exp cardiac surgical procedures/	220390
16	cardiopulmonary bypass/	23730
17	cardioplegic solutions/	2308
18	cardiosurg$.tw.	1110
19	cardiomyoplast$.tw.	846

20	((aortocoronary or atriopulmonary or cardia$ or coronary or heart or myocardia$) adj2 (bypass$ or operat$ or surg$ or transplant$)).tw.	146162
21	((arterial$ or atrial$ or double) adj2 switch$).tw.	2285
22	annuloplast$.tw.	3820
23	valvuloplast$.tw.	4788
24	(valv$ adj2 (implant$ or operat$ or reduc$ or repair$ or replace$ or short$ or surg$)).tw.	55359
25	((fontan or jatene or maze or mustard or norwood or rastelli or ross or senning) adj2 (operat$ or procedure? or repair$ or surg$ or technique?)).tw.	8328
26	pericard?ectom$.tw.	1611
27	pericard?otom$.tw.	720
28	(induce$ adj2 (heart or cardia$ or coronary or myocardia$) adj2 arrest$).tw.	839
29	cardiopleg$.tw.	7095
30	micropleg$.tw.	27
31	(priming adj2 (fluid? or mixture? or preparation? or solution?)).tw.	426
32	intracardi$.tw.	15759
33	intra cardi$.tw.	786
34	or/15-33	329278
35	and/14,34	337
36	exp animals/ not humans/	4752348
37	35 not 36	260
38	limit 37 to english language	231

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: November 5, 2020
- Limits: Humans (search hedge); English language
- Number of results: 635
- Note: Did not include ‘glucose’ as an Emtree term because retrieved too many irrelevant results

1	‘sodium dihydrogen phosphate'/de	5158
2	((sodium* OR monosodium* OR disodium* OR trisodium* OR natri*) NEAR/2 (phosphat* OR biphosphat*)):ti,ab,tn	9825
3	‘sodiumphosphat*':ti,ab,tn	443
4	‘citrate sodium'/de	5398
5	‘citrate disodium'/de	128
6	‘citrate trisodium'/de	1003
7	((sodium* OR monosodium* OR disodium* OR trisodium* OR natri*) NEAR/2 citr*):ti,ab,tn	6514
8	‘citric acid'/de	41462
9	(citric* NEAR/2 acid*):ti,ab,tn	17295
10	‘citronensaure':ti,ab,tn	6
11	‘dextroglucose':ti,ab,tn	7
12	‘dextro glucose':ti,ab,tn	0
13	‘dglucose':ti,ab,tn	10700
14	‘d glucose':ti,ab,tn	25176
15	‘dextrose':ti,ab,tn	16413
16	‘buckberg':ti,ab	124
17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	107101
18	‘heart surgery'/exp	402114
19	‘cardiopulmonary bypass'/de	49096
20	‘intracardiac drug administration'/exp	6759

21	‘cardioplegic agent'/de	2047
22	‘cardiosurg*':ti,ab	1933
23	‘cardiomyoplast*':ti,ab	1010
24	((aortocoronary OR atriopulmonary OR cardia* OR coronary OR heart OR myocardia*) NEAR/2 (bypass* OR operat* OR surg* OR transplant*)):ti,ab	213431
25	((arterial* OR atrial* OR double) NEAR/2 switch*):ti,ab	3314
26	‘annuloplast*':ti,ab	5588
27	‘valvuloplast*':ti,ab	7241
28	(valv* NEAR/2 (implant* OR operat* OR reduc* OR repair* OR replace* OR short* OR surg*)):ti,ab	85085
29	((fontan OR jatene OR maze OR mustard OR norwood OR rastelli OR ross OR senning) NEAR/2 (operat* OR procedure$ OR repair* OR surg* OR technique$)):ti,ab	12186
30	‘pericard$ectom*':ti,ab	2462
31	‘pericard$otom*':ti,ab	1066
32	(induce* NEAR/2 (cardia* OR coronary OR heart OR myocardia*) NEAR/2 arrest*):ti,ab	1541
33	‘cardiopleg*':ti,ab	8954
34	‘micropleg*':ti,ab	33
35	(priming NEAR/2 (fluid$ OR mixture$ OR preparation$ OR solution$)):ti,ab	643
36	‘intracardi*':ti,ab	26006
37	‘intra cardi*':ti,ab	1849
38	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37	505022
39	#17 AND #38	896
40	[animals]/lim NOT [humans]/lim	6115649
41	#39 NOT #40	718
42	#39 NOT #40 AND [english]/lim	635

Appendix 2.1. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

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

2. Do you prescribe or administer sodium phosphate monobasic anhydrous / citric acid / sodium citrate / d-glucose with or without adenine (CPD, CP2D, or CPDA) to your patients?
    - Yes
    - No
3. Do you prescribe or administer sodium phosphate monobasic anhydrous / citric acid / sodium citrate / d-glucose with or without adenine (CPD, CP2D, or CPDA) by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Cardioplegia solution
    - Organ preservation solution
    - None of the above
4. I prescribe or administer sodium phosphate monobasic anhydrous / citric acid / sodium citrate / d-glucose with or without adenine (CPD, CP2D, or CPDA) for the following conditions or diseases: (check all that apply)
    - Cardioplegia in surgical cardiac procedures
    - Organ preservation during transplantation
    - Other (please explain) _____
5. I use compounded sodium phosphate monobasic anhydrous / citric acid / sodium citrate / d-glucose with or without adenine (CPD, CP2D, or CPDA) because: (check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
    - Patient allergies prevent me from using commercially available products (please explain) _____
    - Patient conditions prevent me from using commercially available products (please explain) _____
    - I am not aware of any commercially available products containing sodium phosphate monobasic anhydrous / citric acid / sodium citrate / d-glucose with or without adenine (CPD, CP2D, or CPDA)
    - Other (please explain) _____
6. Do you stock non-patient-specific compounded sodium phosphate monobasic anhydrous / citric acid / sodium citrate / d-glucose with or without adenine (CPD, CP2D, or CPDA) at your practice?

- Yes
- No
- I'm not sure

7. I obtain compounded sodium phosphate monobasic anhydrous / citric acid / sodium citrate / d-glucose with or without adenine (CPD, CP2D, or CPDA) 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) _____
8. 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) _____
9. What degree do you hold? (check all that apply)
    - Doctor of Medicine (MD)
    - Doctor of Osteopathic Medicine (DO)
    - Doctor of Medicine in Dentistry (DMD/DDS)
    - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - Naturopathic Doctor (ND)
    - Nurse Practitioner (NP)
    - Physician Assistant (PA)
    - Other (please describe) _____

Appendix 2.2. Survey instrument for pharmacy roundtable prequestionnaire

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

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

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

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

Appendix 3. Survey distribution to professional associations

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

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