Summary Report

Citric acid anhydrous

Prepared for:

Food and Drug Administration
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
CPD	Citrate phosphate dextrose
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
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 citric acid anhydrous (UNII code: XF417D3PSL), 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 citric acid anhydrous 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 citric acid anhydrous 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 citric acid anhydrous 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

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

Citric acid anhydrous was nominated for anticoagulation during cardioplegia via an intracardiac injection solution.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of citric acid anhydrous.[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 citric acid anhydrous 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 citric acid anhydrous; name variations of citric acid anhydrous 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 citric acid anhydrous. 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: citric acid anhydrous, sodium citrate, sodium phosphate or dextrose, and surgical cardiac procedures, cardioplegia or intracardiac administration (refer to Appendix 1 for full search strategies). Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on April 11, 2020. The reference lists of relevant systematic reviews and meta-analyses were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on April 11, 2020 for clinical practice guidelines that recommended the use of citric acid anhydrous and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which citric acid anhydrous 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 citric acid anhydrous was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage

form, ROA, or combination that was not nominated. Studies in which citric acid anhydrous 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 citric acid anhydrous; setting; total number of patients; number of patients who received citric acid anhydrous; patient population; indication for use of citric acid anhydrous; dosage form and strength; dose; ROA; frequency and duration of therapy; use of citric acid anhydrous in a combination product; use and formulation of citric acid anhydrous in a compounded product; use of citric acid anhydrous 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 citric acid anhydrous was used in a clinical setting. The systematic literature review and indication from the nomination were reviewed to identify the following medical specialties that would potentially use citric acid anhydrous: cardiac surgery. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and 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 entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of citric acid anhydrous 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 Year 1 were not contacted to distribute the project Year 2 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

- Citric acid anhydrous is not available as an FDA-approved product in the nominated dosage form and ROA.
- Citric acid anhydrous is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for citric acid anhydrous.
- Citric acid anhydrous is available in the nominated dosage form and ROA in Canada and Namibia.

Table 1. Currently approved products – US

No approved products in the US

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]
Citric acid / Dextrose / Sodium citrate dihydrate / Sodium phosphate monobasic	3.27 g/L / 25.5 g/L / 26.3 g/L / 2.51 g/L	Solution	–	Canada	Ethical	8/22/2016
Citric acid / Acid sodium phosphate dihydrate / Glucose / Sodium citrate	0.327 g / 0.251 g / 2.55 g / 2.63 g	Blood bag	–	Namibia	–	6/14/1972

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 828 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 633 titles and abstracts were screened. After screening, the full text of 57 articles were reviewed. Finally, 1 study was included. Fifty-six studies were excluded for the following reasons: wrong study design (25 studies); wrong substance (24); wrong combination (4); wrong indication (3).

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

Characteristics of included studies

The 1 included study was published in 2011. It was an experimental study conducted in Iran, with 50 participants.

Outcome measures included: left ventricular ejection fraction (EF), serum malondialdehyde, total antioxidant capacity, and superoxide dismutase.

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

Use of citric acid anhydrous

Twenty-five patients received citric acid anhydrous as an experimental treatment for cardioplegia in coronary artery bypass graft surgery, administered as an injection in doses ranging from 30-100 mL. Duration of treatment was for the duration of surgery.

Refer to Table 9 for summaries of dosage by indication.

Citric acid anhydrous was not used as a compounded product, but it was used in a combination product (refer to Table 8).

In the 1 included study, the authors' conclusion stated that the combination solution was effective in improving the antioxidant status but had little effect in reducing other markers of oxidative stress. Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

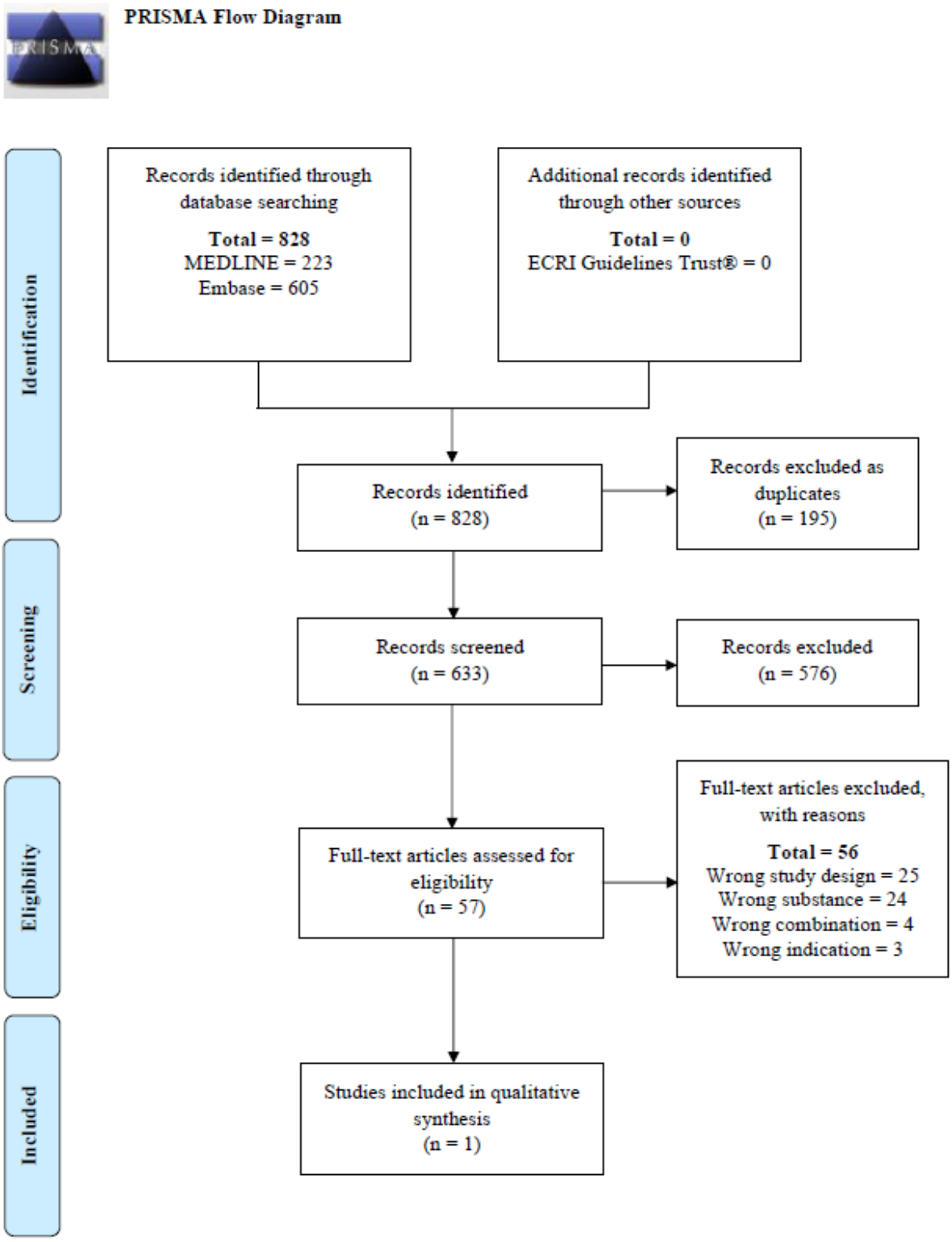
In addition to the 1 included study, 5 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of citric acid anhydrous.

Cardiopulmonary bypass procedure is routinely performed for coronary artery disease, but ischemia during the procedure and reperfusion injury following ischemia can lead to severe tissue damage.[8] According to Yaghoubi et al, "ischemic heart is prone to rapid flow of calcium effusion into the [cardiomyocytes] that occurs in the initial minutes after aortic clamping removal or in the last minutes of cardiopulmonary bypass."[8]

Cardioplegia is "an important strategy to facilitate cardiac surgery while limiting intraoperative myocardial injury"[9] by "inducing electromechanical arrest to allow access to a still and bloodless field".[10] Increased ionized calcium levels in the heart can be easily controlled by using cardioplegic solutions containing large amounts of potassium or magnesium that inhibits calcium entry into cells.[8] The concentration of ionized calcium can also be reduced using calcium channel blockers, sodium

hydrogen ion exchange inhibitors and chelators such as the citrate phosphate dextrose (CPD) combination, a solution of citric acid, sodium citrate, sodium phosphate and dextrose.[8] There are many cardioplegic solutions that contain CPD in combination with other ingredients, such as the Buckberg solution, which is a dextrose-based solution with tromethamine, citrate-phosphate-2-dextrose, and potassium chloride; glutamate and aspartate are added during reperfusion.[11-13]

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	0
Experimental[8]	1
Observational	0

Table 4. Number of studies by country

Country	**Number of Studies**
Iran[8]	1
	Total US: 0 Total Non-US Countries: 1

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
Yaghoubi *et al.*, 2011, Iran[8]	Double blind clinical trial	50 In-patients undergoing elective coronary artery bypass graft surgery (60%, mean 62.3 y ± 9.1)	• Citrate phosphate dextrose (25) • Pure blood (25)	Left ventricular ejection fraction (EF), serum malondialdehyde, total antioxidant capacity, superoxide dismutase	A solution of citrate phosphate dextrose is effective in improving the antioxidant status but has little effect in reducing other markers of oxidative stress.

[a]As defined by authors.

Table 6. Dosage by indication – US

No studies identified

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Cardioplegia in coronary artery bypass graft surgery	30-100 mL	–	Solution	Injection	For the duration of surgery

Abbreviation: "–", not mentioned.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Citric acid anhydrous / Sodium citrate dihydrate / Sodium phosphate / D-glucose[8] – injection solution	1

Table 9. Compounded products – US

No studies identified

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Two SMEs discussed citric acid anhydrous. 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.

Results of survey

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

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which citric acid anhydrous prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded citric acid anhydrous

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded citric acid anhydrous

No respondents to survey distributed via professional medical associations

CONCLUSION

Citric acid anhydrous was nominated for inclusion on the 503B Bulks List as an intracardiac injection solution to be used as an anticoagulant during cardioplegia. Citric acid anhydrous is available in the nominated dosage form and ROA in Canada and Namibia.

From the literature review and interviews conducted, citric acid anhydrous is used for cardioplegia. From the 1 included study, the authors concluded that the CPD combination solution was effective in improving the antioxidant status but had little effect in reducing other markers of oxidative stress. SMEs provided background information on the use of cardioplegia in cardiac procedures and commonly used solutions. In regard to having citric acid in the cardioplegia solution, one SME said that it is not used for cardioplegia but more as an anticoagulant. Since this SME gives patients heparin before giving cardioplegia, they felt that no additional anticoagulants were needed.

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

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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 April 10, 2020
- Date last searched: April 11, 2020
- Limits: Humans (search hedge); English language
- Number of results: 223

1	citric acid/	10585
2	sodium citrate/	749
3	(citric$ adj2 acid$).tw.	12758
4	citronensaure.tw.	0
5	((sodium or monosodium or trisodium) adj2 citrate).tw.	3820
6	natrii citras.tw.	0
7	natrocitral.tw.	0
8	dextroglucose.tw.	3
9	dextro glucose.tw.	0
10	dglucose.tw.	21
11	d glucose.tw.	20622
12	dextrose.tw.	12063
13	((sodium or monosodium) adj2 (phosphate or biphosphate)).tw.	6036
14	sodiumphosphate.tw.	4
15	(citrate adj2 phosphate).tw.	1177
16	buckberg.tw.	62
17	or/1-16	61745
18	exp cardiac surgical procedures/	215175
19	cardiopulmonary bypass/	23441
20	cardioplegic solutions/	2288

21	cardiosurg$.tw.	1101
22	cardiomyoplast$.tw.	844
23	((aortocoronary or atriopulmonary or cardia$ or coronary or heart or myocardia$) adj2 (bypass$ or operat$ or surg$ or transplant$)).tw.	142209
24	((arterial$ or atrial$ or double) adj2 switch$).tw.	2212
25	annuloplast$.tw.	3693
26	valvuloplast$.tw.	4679
27	(valv$ adj2 (implant$ or operat$ or reduc$ or repair$ or replace$ or short$ or surg$)).tw.	52859
28	((fontan or jatene or maze or mustard or norwood or rastelli or ross or senning) adj2 (operat$ or procedure? or repair$ or surg$ or technique?)).tw.	8085
29	pericard?ectom$.tw.	1570
30	pericard?otom$.tw.	706
31	(induce$ adj2 (heart or cardia$ or coronary or myocardia$) adj2 arrest$).tw.	810
32	cardiopleg$.tw.	7012
33	micropleg$.tw.	26
34	(priming adj2 (fluid? or mixture? or preparation? or solution?)).tw.	422
35	intracardi$.tw.	15360
36	intra cardi$.tw.	746
37	or/18-36	320503
38	and/17,37	329
39	exp animals/ not humans/	4689514
40	38 not 39	252
41	limit 40 to english language	223

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: April 11, 2020
- Limits: Humans (search hedge); English language
- Number of results: 605

1	citric acid'/de	40335
2	citrate sodium'/de	5281
3	sodium dihydrogen phosphate'/de	5059
4	(citric* NEAR/2 acid*):ti,ab,tn	16679
5	citronensaure':ti,ab,tn	6
6	((sodium OR monosodium OR trisodium) NEAR/2 citrate):ti,ab,tn	5971
7	natrii citras':ti,ab,tn	0
8	natrocitral':ti,ab,tn	0
9	dextroglucose':ti,ab,tn	7
10	dextro glucose':ti,ab,tn	0
11	dglucose':ti,ab,tn	210
12	d glucose':ti,ab,tn	24703
13	dextrose':ti,ab,tn	15906
14	((sodium OR monosodium) NEAR/2 (phosphate OR biphosphate)):ti,ab,tn	7987
15	sodiumphosphate':ti,ab,tn	18
16	(citrate NEAR/2 phosphate):ti,ab,tn	1584
17	buckberg':ti,ab	121
18	#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 OR #17	103019
19	heart surgery'/exp	389181
20	cardiopulmonary bypass'/de	47443
21	intracardiac drug administration'/exp	6741
22	cardioplegic agent'/de	2015

23	cardiosurg*':ti,ab	1722
24	cardiomyoplast*':ti,ab	1001
25	((aortocoronary OR atriopulmonary OR cardia* OR coronary OR heart OR myocardia*) NEAR/2 (bypass* OR operat* OR surg* OR transplant*)):ti,ab	206184
26	((arterial* OR atrial* OR double) NEAR/2 switch*):ti,ab	3224
27	annuloplast*':ti,ab	5348
28	valvuloplast*':ti,ab	7059
29	(valv* NEAR/2 (implant* OR operat* OR reduc* OR repair* OR replace* OR short* OR surg*)):ti,ab	81182
30	((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$)):ti,ab	11847
31	pericard$ectom*':ti,ab	2393
32	pericard$otom*':ti,ab	1045
33	(induce* NEAR/2 (cardia* OR coronary OR heart OR myocardia*) NEAR/2 arrest*):ti,ab	1495
34	cardiopleg*':ti,ab	8793
35	micropleg*':ti,ab	32
36	(priming NEAR/2 (fluid$ OR mixture$ OR preparation$ OR solution$)):ti,ab	631
37	intracardi*':ti,ab	23922
38	intra cardi*':ti,ab	1771
39	#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 OR #38	488895
40	#18 AND #39	864
41	[animals]/lim NOT [humans]/lim	6015158
42	#40 NOT #41	688
43	#40 NOT #41 AND [english]/lim	605

Appendix 2. Survey instrument

Welcome. We want to understand your clinical use of compounded citric acid / d-glucose / sodium citrate / sodium phosphate. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly,
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

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)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer citric acid / d-glucose / sodium citrate / sodium phosphate as a combination product to your patients?

   - o Yes
   - o No

3. Do you prescribe or administer citric acid / d-glucose / sodium citrate / sodium phosphate as a combination product for the following conditions or diseases? (check all that apply)

   - o Anticoagulant for cardioplegia
   - o Other (please describe) _____

4. I prescribe or administer citric acid / d-glucose / sodium citrate / sodium phosphate as a combination product with my patients as the following: (check all that apply)

   - o FDA-approved drug product
   - o Compounded drug product
   - o Over-the-counter drug product
   - o Dietary supplement (e.g. vitamin or herbal supplement sold in retail stores)
   - o Other (please explain) _____

5. I use compounded citric acid / d-glucose / sodium citrate / sodium phosphate because: (check all that apply)

    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain)_____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing citric acid / d-glucose / sodium citrate / sodium phosphate.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded citric acid / d-glucose / sodium citrate / sodium phosphate at your practice?

    - o Yes
    - o No
    - o I'm not sure

7. I obtain compounded citric acid / d-glucose / sodium citrate / sodium phosphate from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations that declined in Year 1 were not contacted in Year 2.