Summary Report

Phosphatidylcholine

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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
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
IV	Intravenous
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 phosphatidylcholine (UNII code: 1DI56QDM62), 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 phosphatidylcholine 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 phosphatidylcholine 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 phosphatidylcholine 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

Phosphatidylcholine was nominated for inclusion on the 503B Bulks List by AnazaoHealth Corporation for atherosclerosis via a 50 mg/mL intravenous (IV) injection.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of phosphatidylcholine.[6-44]

The reason provided for nomination to the 503B Bulks List is because there is no FDA-approved drug product that includes this drug substance.

METHODOLOGY

Background information

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

phosphatidylcholine. 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 three concepts: phosphatidylcholine; intravenous or parenteral administration; and therapeutic use for atherosclerosis or hyperlipidemia (refer to Appendix 1 for full search strategies). Results were limited to human studies in English language. Searches were conducted on January 12, 2021. In addition, the ECRI Guidelines Trust® repository was searched on January 12, 2021 for clinical practice guidelines that recommended the use of phosphatidylcholine 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 phosphatidylcholine 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 phosphatidylcholine was used as: a dosage form, ROA, or combination that was not nominated. Studies in which phosphatidylcholine 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 phosphatidylcholine; setting; total number of patients; number of patients who received phosphatidylcholine; patient population; indication for use of phosphatidylcholine; dosage form and strength; dose; ROA; frequency and duration of therapy; use of phosphatidylcholine in a combination product; use and formulation of phosphatidylcholine in a compounded product; use of phosphatidylcholine 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 phosphatidylcholine was used in a clinical setting. The systematic literature review and the indication from the nomination were reviewed to identify medical specialties that would

potentially use phosphatidylcholine. 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 phosphatidylcholine 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

- Phosphatidylcholine is not available as an FDA-approved product in the nominated dosage form and ROA.
- Phosphatidylcholine is not available as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for phosphatidylcholine.
- Phosphatidylcholine is not available in the nominated dosage form and ROA in any of the foreign medical registries searched.

Table 1. Currently approved products – US

No approved products in the US

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

No approved products in the selected non-US countries and regions

Results of literature review

Study selection

Database searches yielded 954 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 801 titles and abstracts were screened. After screening, the full text of 43 articles was reviewed. Finally, 1 study was included. Forty-three studies were excluded for the following reasons: wrong study design (36 studies); wrong dosage form or ROA (6); unable to obtain full text (1).

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

Characteristics of included studies

There was 1 included 1986 experimental study from Italy.

A total of 45 patients participated in the included study.

Outcome measures differed among the included studies and included: total cholesterol, high-density lipoprotein, and low-density lipoprotein levels.

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

Use of phosphatidylcholine

Fifteen patients received phosphatidylcholine as a treatment for hyperlipoproteinemia, administered 250 mg IV daily for 20 days.

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

Phosphatidylcholine was not used as a compounded product, nor was it used in a combination product (refer to Tables 8-10).

In the 1 study, the authors' conclusions did not address the use of phosphatidylcholine.[45] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

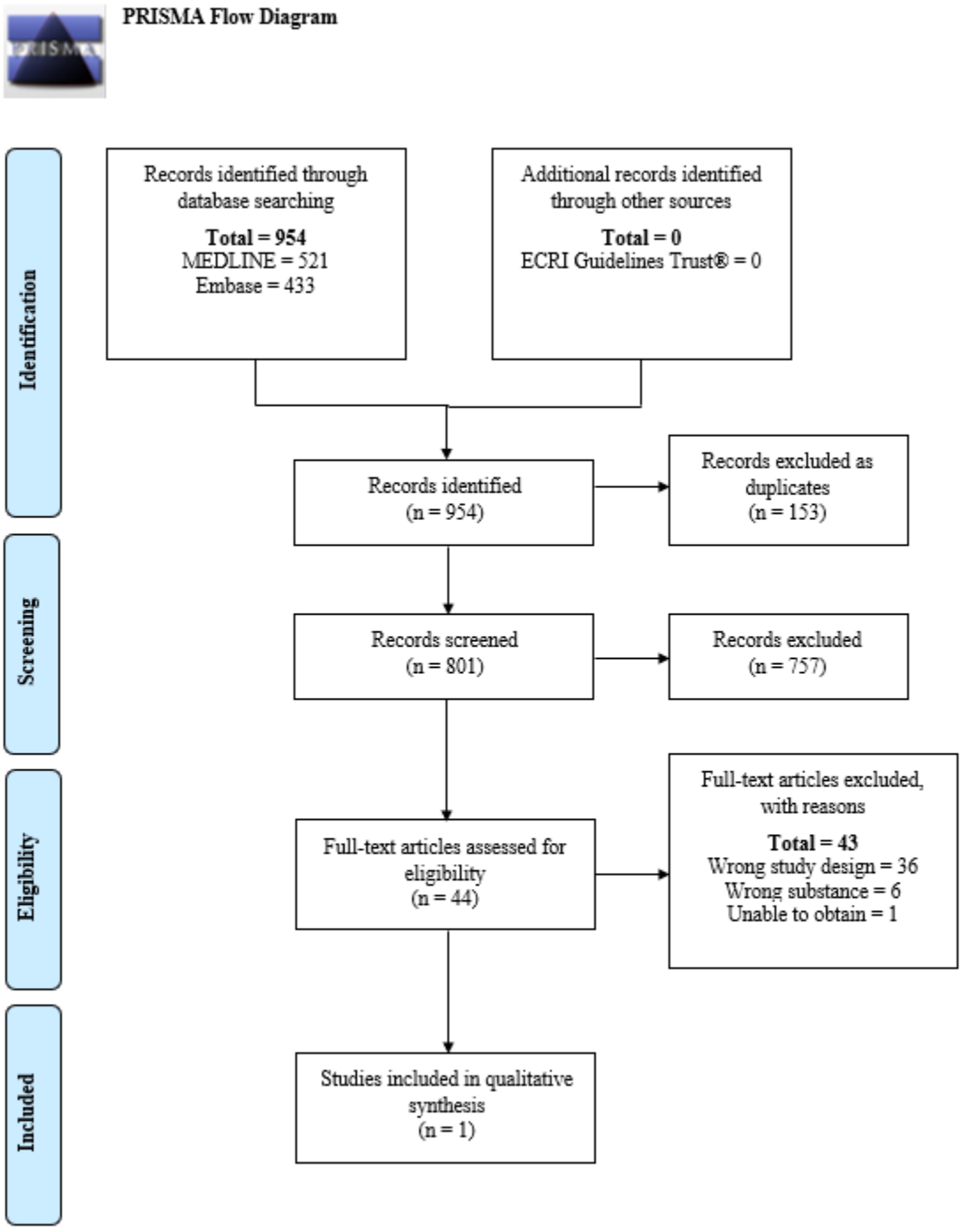
In addition to the 1 included study, 6 additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of phosphatidylcholine.

Phosphatidylcholine is used with deoxycholate as an injection for lipolysis.[46] Phosphatidylcholine, a phospholipid, is poorly water soluble so sodium deoxycholate is used to improve the solubility.[47] In Europe, South America, and South Africa, Lipostabil®, which contains soy-derived phosphatidylcholine 5% and sodium deoxycholate 2.5%, is an intravenous injection used to treat numerous fat-related disorders such as atherosclerosis, hyperlipidemia, angina pectoris, and diabetic angiopathy.[47,48] In the US, there is no pharmaceutical grade injectable phosphatidylcholine with deoxycholate available.[47] Compounding pharmacies have produced formulations, usually phosphatidylcholine 5% with sodium deoxycholate 4.2-4.75% or sodium deoxycholate 1-5% alone, similar to Lipostabil®.[47] While early publications hypothesized phosphatidylcholine was the active ingredient responsible for reducing fat in Lipostabil®, it has been found that sodium deoxycholate alone has comparable effects to phosphatidylcholine with sodium deoxycholate when injected "into lipomas, abdominal, submental, and hip fat."[47] A study by Duncan *et al* that investigated phosphatidylcholine's effect on adipocytes was the first to reveal that phosphatidylcholine has "no adipolytic or lipolytic effects."[47] However, phosphatidylcholine does seems to "reduce the morbidity of the procedure by buffering the ablative effects of [sodium deoxycholate] on tissue."[47] Sodium deoxycholate concentrations >1% alone "[produced] profound inflammation, prolonged nodularity, and potentially, skin necrosis" whereas these effects were less likely to appear when sodium deoxycholate (up to 4.75%) was used in combination with phosphatidylcholine.[47]

There have been several studies that used IV phosphatidylcholine. In a 1990 Spain study by Terminella *et al*, 20 atherosclerotic patients with signs of chronic cerebrovascular insufficiency were split into 2 groups of 10 to evaluate "hematic and plasmatic viscosimetric values at different shear rates, red cell deformability, fibrinogenemia, lipidemia, and hematocrit."[49] The first group received oral nimodipine 30 mg three times a day for 30 days while the second group was given IV phosphatidylcholine 500 mg/day for the first 10 days and then 400 mg three times a day orally for the remaining 20 days.[49] Terminella *et al* found that both drugs decreased hemorheological parameters studied, and phosphatidylcholine appeared to be "effective on plasmatic viscosity and lipidemia in the early phase of the treatment."[49] In another 1992 study by Cantafora *et al*, IV phosphatidylcholine's effect on insulin receptor processing and erythrocyte lipid composition in cirrhosis patients was investigated.[14] Thirteen cirrhotic patients were given IV phosphatidylcholine 2 g/day for 3 days. Cantafora *et al* found that the erythrocyte cholesterol to phospholipid molar ratio was decreased while the portion of polyunsaturated fatty acids and arachidonic acid increased after treatment.[14] Surface insulin receptors also "showed an improvement in down regulation capabilities that [correlated] with the changes in lipid composition of cell membranes induced by IV infusion of polyunsaturated phosphatidylcholine."[14] Cantafora *et al* concluded that these findings in insulin target cells could potentially open new perspectives for treating diabetes mellitus.[14] In a 1995 study by Klimov *et al*, 100 patients with type IIB hyperlipoproteinemia and ischemic heart disease were equally split into 2 groups for a 6 month treatment with nicotinic acid 1.5 g/day or Lipostabil®.[23] Patients in the

Lipostabil® group were given 0.5 g/day essential phospholipids IV for 2 weeks and 6 capsules of Lipostabil® 300 Forte/day for the remaining 5.5 months.[23] Both groups had similar reductions in total cholesterol, low-density lipoprotein cholesterol, triglyceride, intensity and number of angina pectoris attacks a week.[23] However, nicotinic acid increased high-density lipoprotein significantly better while Lipostabil significantly increased patients' working capacity in the veloergometric test.[23] Klimov *et al* concluded that "Lipostabil is a preferable alternative in the treatment of patients with moderate, dietary noncorrigible hyperlipoproteinemia IIb and ischemic heart disease."[23]

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
Observational	0
Experimental[45]	1

Table 4. Number of studies by country

Country	**Number of Studies**
Italy[45]	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
Coto *et al*., 1986, Italy[45]	Controlled double blind study	45 Patients with hyperlipoproteinemia • Coenzyme A (50%, mean 53 y ± 10.4) • Phosphatidylcholine (60%, mean 54 y ± 11.6) • Placebo (66.7%, mean 54 y ± 9.1)	• Coenzyme A (15) • Phosphatidylcholine (15) • Intravenous placebo (15)	Total cholesterol, high-density lipoprotein, and low-density lipoprotein levels	"These findings, although in a limited number of patients, suggest that [coenzyme A] is effective in decreasing plasma lipid levels. These results warrant evaluation of the effect of [coenzyme A] in a larger and more selected patient population over a longer time period to define better the role of [coenzyme A] in certain forms of primary hyperlipoproteinaemia and to achieve a more detailed analysis of the compound's proven antidyslipidaemic action."

[a]As defined by authors.

Table 6. Dosage by indication – US

No US studies were included

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Hyperlipoproteinemia[45]	250 mg/day	250 mg	–	Intravenous	20 days

Abbreviation: "–", not mentioned.

Table 8. Number of studies by combination

No combination products were nominated

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. Four SMEs discussed phosphatidylcholine. Amongst these 4 SMEs, there were 2 medical doctors, 1 naturopathic doctor, and 1 nurse practitioner. The SMEs specialized and/or were board-certified in cardiology, integrative medicine, naturopathy, working in consultant, private practice, community hospital, and academic medical centers. The SMEs had been in practice for 8 to 30 years.

One SME stated that most of the clinical data for phospholipid use in cardiovascular indications comes from Europe, especially Germany. Phosphatidylcholine repairs cell membranes and works via a process called phospholipid exchange, in which phosphatidylcholine after infused will go to the cell membranes and replace the oxidized lipid in the lipid bilayer. Because lipoproteins are formed in a similar way as a cell membrane, this reduces the inflammatory components of very-low-density lipoprotein, low-density lipoprotein, and high-density-lipoprotein membranes. This changes the lipid profile via a forward feeding mechanism. Another SME added that certain enzymes are activated such as "lecithin cholesterol acyltransferase, which is necessary to prepare cholesterol in plaque to be taken off by HDL [high-density lipoprotein] and then be eliminated through the liver." A couple of SMEs have not used phosphatidylcholine for a cardiovascular indication; one SME stated that for the cardiovascular specialty practices in North America they know of that use phosphatidylcholine, it does help with the lipid numbers if used regularly. One SME uses the combination phosphatidylcholine and deoxycholic acid (Plaquex®) from Anazao for cardiovascular diseases such as atherosclerosis and in patients who have contraindications to doing bypass surgery and/or angioplasty; the addition of deoxycholic acid helps make the product soluble and together they help remove cholesterol and calcium deposits. This SME starts the patients out on a 1000 mg (20 mL out of the 50 mL vial) dose for the first treatment, given over 1.5 hours. The product can only be dissolved in glucose or dextrose 5% in water. If everything is fine with the first treatment, the rest of the product remaining in the vial is given for the second treatment (usually on the third or fourth day after the first treatment). After that, the full dose 2500 mg (50 mL vial) appropriately dissolved, can be given 2-3 times a week with a day in between each treatment. However, there are some patients in which treatments are done every day or 6 days a week because they had a limited amount of time and/or flew in from another country. The number of treatments needed depends on the severity of the patient's problem. For mild stenosis, about 20-25 treatments and for severe stenosis in the 85-90% range, maybe about 40-60 treatments. Most patients start to feel some relief after a few treatments because phosphatidylcholine is incorporated into the cell membranes of platelets and red blood cells, thereby reducing platelet aggregation, and increasing red blood cells' flexibility so that they can pass

through tight capillaries easier. Because the buildup of plaque will continue due to the underlying reason, patients may need to come back for a second series of treatments or depending on the patient's status, may be able to be on a maintenance therapy of 1-2 IVs per month. All treatments are done in a doctor's office unless the doctor prescribes it and the patient hires a nurse to administer it. For some patients, using this treatment could reduce or eliminate the need for other medications. This SME also commented that other doctors have said that this treatment is "saving [patient's] lives or their limbs. [For example], there was one [patient] who started to have gangrene in one of his legs and it was inoperable, and the surgeon wanted to amputate it. [This patient] did the treatment and [he is] out playing golf again…So those are patients who have no other option. So [it is] really a very important treatment to keep ongoing."

Similarly for neurodegenerative diseases such as multiple sclerosis, peripheral neuropathy, and other neuro-inflammatory conditions in which the blood-brain barrier has been damaged such as post-radiation or other chronic inflammatory conditions, the chronic inflammation causes the lipid bilayer to become more inflamed and changes the lipid components. The phospholipid lipid tails will "migrate towards more inflammatory forms of the lipid component," such as phosphatidylcholine and maybe phosphatidylserine. One SME stated when phosphatidylcholine is used with other medications, they have seen patients have symptomatic reversals and sometimes less anxiety, pain, and/or antidepressant medications are needed. Because there are many human cells, it takes a while for phosphatidylcholine to make a clinical difference. One SME expressed it could take 30-40 infusions over the course of 6 plus months and said that this is a "pretty regular treatment in the beginning with the very ill." Depending on comorbidities and that the patient's inflammatory levels are lower over time, most patients do not need to continue the infusions and can take oral phosphatidylcholine or phospholipids to maintain their levels. Some patients who have rapid multiple sclerosis progression, advanced seizure disorders, or a triggering event such as receiving radiation again in which there is not a way to down-regulate the underlying disease may need to be on the infusions for longer. Another SME who uses phosphatidylcholine and sodium deoxycholate (Plaquex®) from Anazao for neurodegenerative diseases has had positive patient outcomes and never had any issues. They do not jump to using phosphatidylcholine in patients with neurologic symptoms only because it is not always possible for IV therapy patients to come into the office twice a week. Patients on the IV treatment stay on the treatment for as long as they would like to. Some patients stop and then start the therapy again when they feel they are getting worse. This SME added that if the patient can afford the treatment since it is not covered by insurance, they do not see a downside. Oral phosphatidylcholine supplements, which are available as a liquid and capsules over-the-counter, are used when possible. One SME commented they had no personal experience with using phosphatidylcholine for neurodegenerative diseases, but since phosphatidylcholine has a hard time crossing the blood-brain barrier, they are not sure how effective it would be for indications such as dementia unless it is a vascular-related problem.

In Europe, there is a brand name phosphatidylcholine drug called Lipostabil® used as an infusion for hyperlipidemia. One SME commented that when drug import laws were different around 20 years ago, European phosphatidylcholine drugs such as Lipostabil®, Essentiale®, Plaquex® used to be imported to the US by pharmacies and redistributed. There were also a few 503As that used to make phosphatidylcholine, but most have stopped now. One SME stated Lipostabil® does not exist anymore in all markets except maybe in Germany and Russia. In the US, a SME commented that the only way to get phosphatidylcholine injection is to have it compounded. This SME who used phosphatidylcholine for cardiovascular indications is concerned facilities might use the wrong type of phosphatidylcholine; they cautioned that the pharmacy needs to know the right phosphatidylcholine product to use because there are about 20-30 different types of phosphatidylcholines. If the wrong phosphatidylcholine is chosen such as one with saturated fatty acid chains, the opposite effect can happen. Also, if phosphatidylcholine is not used in a high enough concentration, it can cause deoxycholic acid to dissociate which could cause

thrombophlebitis and hemolysis. There are several commercially available oral phosphatidylcholine or mixed phospholipid supplements. One SME expressed that the oral product could do the same things as the IV product except remove plaque because the oral product does not stay long enough in the places it would need to be with about 90% of the oral product ending up in the liver after the first bypass.

Other indications mentioned by SMEs include the use of phosphatidylcholine in liver disease, kidney disease, pancreatitis, and pregnant women who have severe problems with nausea and pre-eclampsia. A SME also commented that oral phosphatidylcholine could help people with stomach issues such as when taking non-steroidal anti-inflammatory drugs because phosphatidylcholine coats the stomach with a surfactant layer. Another SME stated that they believe phosphatidylcholine is "used for surfactant production in immature lung membranes." There are also some doctors who use subcutaneous phosphatidylcholine injections in lipo dissolve treatment. One SME expressed that "[phosphatidylcholine] has a wide range of application and it has rejuvenating effects because it really fixes all the cell membranes."

Overall, 2 SMEs have had positive experiences with using phosphatidylcholine in neurodegenerative diseases, 1 SME in cardiovascular diseases, while 1 SME had no experience using phosphatidylcholine.

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

One person responded to the survey distributed via professional medical associations and available on the project website; refer to Table 11 for respondent characteristics.

The 1 respondent used phosphatidylcholine as an intravenous injection to treat atherosclerosis. The respondent used compounded phosphatidylcholine due to lack of commercial products in an appropriate dosage form, strength or combination, patient allergies preventing using of commercial products, and other patient conditions preventing use of commercial products. Refer to Table 13 for reasons for using compounded phosphatidylcholine.

The respondent did stock non-patient-specific compounded phosphatidylcholine at their practice. The respondent purchased, or had the patient purchase, the product from a compounding pharmacy or outsourcing facility. Refer to Table 14 for how respondents obtained compounded phosphatidylcholine.

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.

Phosphatidylcholine was not included on the prequestionnaire (refer to Table 18).

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	Responses, n (N=1)
Doctor of Medicine (MD)	0
Doctor of Osteopathic Medicine (DO)	0
Doctor of Medicine in Dentistry (DMD/DDS)	0
Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)	0
Naturopathic Doctor (ND)	1
Doctor of Nursing (DNP) or Master of Nursing (MSN)	0

Physician Assistant (PA)	0
Practice Setting	**Responses, n (N=1)**
Physician office or private practice	1
Outpatient clinic	0
Hospital or health system	0
Academic medical center	0
Emergency room	0
Operating room	0

Table 12. Conditions for which phosphatidylcholine prescribed or administered

Condition	Responses, n (N=2)[a]
Atherosclerosis	1
Other[b]	1

[a]Survey respondents allowed to select multiple conditions.
[b]Condition not specified.

Table 13. Reasons for using compounded phosphatidylcholine

Reason	Responses, n (N=3)[a]
Commercial product not available in desired dosage form, strength, or combination	1
Patient allergies prevent use of commercial products	1
Patient conditions prevent use of commercial products	1
No commercial products	0

[a]Survey respondents allowed to select multiple reasons.

Table 14. Use of non-patient-specific compounded phosphatidylcholine

Do you stock non-patient-specific compounded phosphatidylcholine at your practice?	Responses, n (N=1)
Yes	1

No	0
Not sure	0
How do you obtain your stock of non-patient-specific compounded phosphatidylcholine?	
Compound yourself at practice	0
Product compounded by in-house pharmacy	0
Purchase from compounding pharmacy	1
Purchase from outsourcing facility	1

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

Phosphatidylcholine was nominated for inclusion on the 503B Bulks List as an IV injection for atherosclerosis. Phosphatidylcholine is not available in the nominated dosage form and ROA in any of the medical registries searched.

From the literature review, the included study used IV phosphatidylcholine for hyperlipoproteinemia. Phosphatidylcholine has also been used with deoxycholate as an injection for lipolysis. In Europe, South America, and South Africa, Lipostabil®, which contains soy-derived phosphatidylcholine 5% and sodium deoxycholate 2.5%, is an intravenous injection used to treat numerous fat-related disorders such as atherosclerosis, hyperlipidemia, angina pectoris, and diabetic angiopathy.[47,48]

From the interviews conducted, 2 SMEs have had positive experiences with using phosphatidylcholine in neurodegenerative diseases, 1 SME in cardiovascular diseases, while 1 SME had no experience using phosphatidylcholine. A SME commented that the only way to get phosphatidylcholine injection in the US is to have it compounded. Another SME noted there were also a few 503As that used to make phosphatidylcholine, but most have stopped now. One SME is also concerned facilities might use the wrong type of phosphatidylcholine; they cautioned that the pharmacy needs to know the right phosphatidylcholine product to use because there are about 20-30 different types of phosphatidylcholines. Also, if the phosphatidylcholine concentration is not high enough, it can cause deoxycholic acid to dissociate which could cause thrombophlebitis and hemolysis. Other indications mentioned by SMEs include the use of phosphatidylcholine in liver disease, kidney disease, pancreatitis, and pregnant women who have severe problems with nausea and pre-eclampsia. Another SME stated that they believe phosphatidylcholine is “used for surfactant production in immature lung membranes.”

From the survey responses, 1 out of 1 respondent used phosphatidylcholine. The most common indication respondents used compounded phosphatidylcholine for was atherosclerosis. Lack of commercial products in an appropriate dosage form, strength or combination, patient allergies preventing using of commercial products, and other patient conditions preventing use of commercial products were some of the reasons for using the compounded phosphatidylcholine product over an FDA-approved product. The 1 respondent reported stocking non-patient specific compounded phosphatidylcholine.

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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 January 8, 2021
- Date last searched: January 12, 2021
- Limits: Humans (search hedge); English language
- Number of results: 521

1	phosphatidylcholines/	31359
2	(cholin$ adj glycerophosph$).tw.	228
3	(cholin$ adj phosph$).tw.	1235
4	(diacyl adj glycerophosph#cholin$).tw.	35
5	diacylglycerophosph#cholin$.tw.	44
6	diacylglycerophosphorylcholin$.tw.	1
7	diacylphosphatidylcholin$.tw.	126
8	fosfatidylcholin*.tw.	0
9	(glycerophosphatidyl adj cholin$).tw.	4
10	glycerophosphatidylcholin$.tw.	76
11	(phosphatidyl adj cholin$).tw.	1800
12	phosphatidylcholin$.tw.	32976
13	or/1-12	52999
14	exp administration, intravenous/	144253
15	infusions, parenteral/	26313
16	injections/	43038
17	inject$.tw.	755604
18	infusion$.tw.	248068
19	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	12392
20	intravenous$.tw.	346556

21	intra venous$.tw.	586
22	intravascular$.tw.	48680
23	intra vascular$.tw.	309
24	or/14-23	1299576
25	exp arteriosclerosis/	180967
26	exp hyperlipidemias/	66702
27	de.fs.	3027921
28	dt.fs.	2267402
29	ad.fs.	1435394
30	tu.fs.	2257937
31	arterioscler$.tw.	15905
32	(arter$ adj2 scler$).tw.	667
33	arterioloscler$.tw.	486
34	atherogen$.tw.	29878
35	atheroma$.tw.	10965
36	atheroscler$.tw.	152950
37	(athero$ adj2 scler$).tw.	176
38	(peripheral arter$ adj2 (disease$ or occlu$)).tw.	17048
39	(vascular$ adj2 scler$).tw.	611
40	hyperlipid?em$.tw.	31520
41	hyperlip?em$.tw.	3009
42	lipid?em$.tw.	799
43	lip?em$.tw.	3070
44	hyperlipoprotein?em$.tw.	4516
45	hypercholesterol?em$.tw.	35170
46	hypercholester?em$.tw.	888

47	hypercholesterin?em$.tw.	201
48	cholesterol?em$.tw.	1393
49	cholester?em$.tw.	85
50	cholesterin?em$.tw.	45
51	hypertriglycerid?em$.tw.	14367
52	triglycerid?em$.tw.	757
53	or/25-52	6083573
54	and/13,24,53	1745
55	exp animals/ not humans/	4775224
56	54 not 55	576
57	limit 56 to english language	521

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: January 12, 2021
- Limits: Humans (search hedge); English language
- Number of results: 433

1	‘phosphatidylcholine'/de	45171
2	(cholin* NEAR/1 glycerophosph*):ti,ab,tn	347
3	(cholin* NEAR/1 phosph*):ti,ab,tn	4275
4	(diacyl NEAR/1 glycerophosphacholin*):ti,ab,tn	0
5	(diacyl NEAR/1 glycerophosphocholin*):ti,ab,tn	32
6	‘diacylglycerophosphacholin*':ti,ab,tn	0
7	‘diacylglycerophosphocholin*':ti,ab,tn	62
8	‘diacylglycerophosphorylcholin*':ti,ab,tn	3
9	‘diacylphosphatidylcholin*':ti,ab,tn	165
10	‘fosfatidylcholin*':ti,ab,tn	0
11	(glycerophosphatidyl NEAR/1 cholin*):ti,ab,tn	4
12	‘glycerophosphatidylcholin*':ti,ab,tn	93
13	(phosphatidyl NEAR/1 cholin*):ti,ab,tn	2303
14	‘phosphatidylcholin*':ti,ab,tn	36629
15	#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	62356
16	‘parenteral drug administration'/de	2269
17	‘intravenous drug administration'/exp	394674
18	‘injection'/exp	248601
19	‘inject*':ti,ab	1121535
20	(parenteral* NEAR/2 (administ* OR deliver* OR infus* OR therap* OR treat*)):ti,ab	19294
21	‘intravenous*':ti,ab	500685
22	‘intra venous*':ti,ab	1488

23	‘intravascular*':ti,ab	70057
24	‘intra vascular*':ti,ab	708
25	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	1837926
26	‘drug dose':lnk	628909
27	‘drug administration':lnk	1788043
28	‘drug therapy':lnk	3999522
29	‘arteriosclerosis'/exp	283060
30	‘hyperlipidemia'/exp	170490
31	‘arterioscler*':ti,ab	27741
32	(arter* NEAR/2 scler*):ti,ab	1466
33	‘arterioloscler*':ti,ab	921
34	‘atherogen*':ti,ab	41249
35	‘atheroma*':ti,ab	17157
36	‘atheroscler*':ti,ab	221480
37	(athero* NEAR/2 scler*):ti,ab	404
38	('peripheral arter*' NEAR/2 (disease* OR occlu*)):ti,ab	27643
39	(vascular* NEAR/2 scler*):ti,ab	1156
40	‘hyperlipid$em*':ti,ab	51431
41	‘hyperlip$em*':ti,ab	5076
42	‘lipid$em*':ti,ab	1701
43	‘lip$em*':ti,ab	4962
44	‘hyperlipoprotein$em*':ti,ab	6006
45	‘hypercholesterol$em*':ti,ab	51746
46	‘hypercholester$em*':ti,ab	1435
47	‘hypercholesterin$em*':ti,ab	412
48	‘cholesterol$em*':ti,ab	2315

49	‘cholester$em*':ti,ab	135
50	‘cholesterin$em*':ti,ab	58
51	‘hypertriglycerid$em*':ti,ab	20830
52	‘triglycerid$em*':ti,ab	1192
53	#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 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52	5120042
54	#15 AND #25 AND #53	1231
55	[animals]/lim NOT [humans]/lim	6150167
56	#54 NOT #55	489
57	#54 NOT #55 AND [english]/lim	433

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 phosphatidylcholine to your patients?
    - Yes
    - No
3. Do you prescribe or administer phosphatidylcholine by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Intravenous injection
    - None of the above
4. I prescribe or administer phosphatidylcholine for the following conditions or diseases: (check all that apply)
    - Atherosclerosis
    - Other (please explain) _____
5. I use compounded phosphatidylcholine 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 phosphatidylcholine
    - Other (please explain) _____
6. Do you stock non-patient-specific compounded phosphatidylcholine at your practice?
    - Yes
    - No
    - I'm not sure
7. I obtain compounded phosphatidylcholine 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

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.