Summary Report

Acetylcysteine

Prepared for:

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

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November 2021

This report was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling $2,342,364, with 100 percent funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the U.S. Government.

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Frequently Used Abbreviations

API	Active pharmaceutical ingredient
EMA	European Medicines Agency
EU	European Union
FDA	US 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 United States Food and Drug Administration (FDA) in evaluating the use of acetylcysteine (UNII code: WYQ7N0BPYC), 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 acetylcysteine 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 health care practitioners were consulted to identify how acetylcysteine 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 acetylcysteine and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Acetylcysteine was nominated for inclusion on the 503B Bulks List by Fagron, the Outsourcing Facilities Association (OFA), and US Compounding.

Acetylcysteine was nominated for treatment of dry eyes caused by meibomian gland dysfunction via a 5-15% ophthalmic solution. In addition, acetylcysteine was nominated for treatment of acetaminophen overdose, administration of anesthesia for procedure, amyloidosis, atelectasis due to mucous obstruction, bronchiectasis, bronchopulmonary disease, chronic bronchitis, chronic disease of the respiratory system, chronic obstructive pulmonary disease (COPD), diagnostic procedure on lower respiratory tract, distal intestinal obstruction syndrome, emphysema, giant papillary conjunctivitis (GPC), mucolysis, nephrotoxicity prophylaxis, pulmonary complications of cystic fibrosis, respiratory complications of surgical procedures, and tracheostomy care via a 10% and 20% inhalation solution and intravenous injection.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of acetylcysteine.[6-23]

Reasons provided for nomination to the 503B Bulks List included:

- There are FDA approved acetylcysteine nebulizer solutions. The excipients and the strength of the FDA approved preparations would make preparing the eye drops too difficult. The pH would need to be adjusted and the excipients could cause irritation.
- Over the counter options with polyvinyl alcohol or hypromellose can have limited effects and have to be administered frequently. Acetylcysteine was shown to be superior to polyvinyl alcohol in a head-to-head comparison. It had the convenience over polyvinyl alcohol of 4 times a day dosing. It also reduced nocturnal discomfort.
- Acetylcysteine has the ability to breakdown mucin that can accumulate in the condition of dry eyes. Cyclosporine acts to decrease inflammation in the eye leading to increased lubrication. Acetylcysteine offers a unique approach to dry eyes that can be effective alternative.
- Acetylcysteine is listed in the Orange Book; therefore, FDA has already determined there is a clinical need for the bulk drug substance.
- The compounded product may be the only product to effectively treat the indication for which it is intended.

- Medication errors are common when acetylcysteine is compounded in the hospital. Allowing outsourcing facilities to compound using the bulk drug substance can reduce medication errors.
- Patient need for dosage form or strength, including greater concentration, that is not available commercially or when ready-to-use packaging is required by a facility.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Manufacturer back order.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of acetylcysteine products in the United States (US) and around the world. The World Health Organization (WHO), 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 acetylcysteine; name variations of acetyclysteine 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, and 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 acetylcysteine. 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: acetylcysteine, and ophthalmic administration or form, or therapeutic use for dry eye (refer to Appendix 1 for full search strategies). A literature review was not conducted for intravenous or inhaled administration due to the availability of FDA-approved products for these ROA. Results were limited to human studies in English language. Searches were conducted on August 10, 2020. In addition, the ECRI Guidelines Trust® repository was searched on August 10, 2020 for clinical practice guidelines that recommended the use of acetylcysteine and provided sufficient information on dosing and administration.

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

Study selection

Studies in which acetylcysteine 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, preclinical 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 acetylcysteine was used as an FDA-approved product in the nominated dosage form or ROA; in a dosage form or ROA that was not nominated; in an unspecified dosage form or ROA; mentioned briefly as a rescue treatment or previously failed treatment. Studies in which acetylcysteine 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 acetylcysteine, setting, total number of patients, number of patients who received acetylcysteine, patient population, indication for use of acetylcysteine, dosage form and strength, dose, ROA, frequency and duration of therapy, use of acetylcysteine in a combination product, use and formulation of acetylcysteine in a compounded product, use of acetylcysteine compared to FDA-approved drugs or other treatments, outcome measures, and authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances acetylcysteine was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify medical specialties that would potentially use acetylcysteine. 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 verbal 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 acetylcysteine 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 for 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

- Acetylcysteine is available as an FDA-approved product in the nominated dosage form and ROA.
- Acetylcysteine was available as an FDA-approved solution for inhalation in combination with isoproterenol that was discontinued, not for reasons of safety or efficacy.
- Acetylcysteine is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for acetylcysteine.
- Acetylcysteine is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Canada, Hong King, Latvia, Namibia, New Zealand, Saudi Arabia, and the UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Acetylcysteine	200 mg/mL	Injectable	Intravenous	Prescription	1/23/2004
Acetylcysteine	10%, 20%	Solution	Inhalation, Oral	Prescription	Prior to 1/01/1982

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

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]
Acetylcysteine	100 mg/mL, 200 mg/mL	Solution	Injection	Abu Dhabi	Active	–
				Australia	Prescription	7/17/2006
				Canada	Marketed	1/26/2018
				Hong Kong	Prescription	11/12/1982
				Latvia	Prescription	5/13/2005
				Namibia	–	11/11/2010
				New Zealand	Prescription	10/26/2006
				Saudi Arabia	Prescription	–
				United Kingdom	Prescription	10/14/1992
Acetylcysteine	60 mg/mL, 100 mg/mL, 200 mg/mL	Solution	Inhalation, Nebulization	Abu Dhabi	Active	–
				Canada	Marketed	1/26/2018
Acetylcysteine	5%	Solution	Ophthalmic	United Kingdom	Prescription	12/17/1992

Abbreviation: –, not provided.

[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 398 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 321 titles and abstracts were screened. After screening, the full text of 74 articles was reviewed. Finally, 12 studies were included. Sixty-two studies were excluded for the following reasons: wrong study design (51 studies), acetylcysteine only mentioned briefly (6), unspecified formulation (2), wrong drug (2), and acetylcysteine not used clinically (1).

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

Characteristics of included studies

The 12 included studies were published between 1968 and 2019. There were 6 experimental studies, 2 observational studies, and 4 descriptive studies. The 12 studies were conducted in the following countries: Austria, Mexico, Turkey, UK, and US.

A total of 166 patients participated in the 12 included studies. The number of patients in each study ranged from 1 to 38.

Outcome measures differed among the included studies and included: resolution of symptoms, occurrence of corneal mucus, conjunctiva injection, presence of mucoid deposits/secretions, patient outcome and satisfaction, tear film thickness, ocular symptoms, fluorescein break-up time values, Schirmer scores, intraocular pressure, visual acuity, healing, histopathologic characteristics, protein deposition, and treatment of superficial punctate keratitis.

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

Use of acetylcysteine

Twenty-nine patients received ophthalmic acetylcysteine as a treatment for keratoconjunctivitis sicca, administered in doses ranging from 1 to 4 times per day, or applied every 2 hours. Duration of treatment ranged from at least 5 days to 2 months. Fifty patients received ophthalmic acetylcysteine as a treatment for dry eye or dry eye syndrome, administered in doses ranging from 1 to 2 times per day, or a total of 2 mL to 8 mL per day. Duration of treatment ranged from 2 days to 993 days. Twenty patients received ophthalmic acetylcysteine as a treatment for meibomian gland dysfunction, administered 4 times per day. Duration of treatment was 1 month. One patient received ophthalmic acetylcysteine as a treatment for keratitis mucosa, administered in doses ranging from 1-2 drops every 20-30 minutes to 4 times per day. Duration of treatment was at least 3.5 months. Two patients received ophthalmic acetylcysteine as a treatment for ocular silver nitrate burn, administered 4 times per day for an unknown duration of treatment. An unknown number of patients received ophthalmic acetylcysteine as a treatment for primary pterygia in a concentration of 10% for an unknown duration of treatment. Nine patients received acetylcysteine as a treatment for protein deposition on contact lenses, administered 4 times per day for a duration of 2 months. An unknown number of patients received ophthalmic acetylcysteine as a treatment for superficial punctate keratitis in a concentration of 10% for an unknown duration of treatment.

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

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

In 7 studies, the authors' concluding statement recommended the use of acetylcysteine for the treatment of dry eye, keratitis mucosa, keratoconjunctivitis sicca, meibomian gland dysfunction, and primary pterygia.[24-30] There were 3 studies where the authors concluded that the use of acetylcysteine required further studies regarding the treatment of dry eye syndrome, meibomian gland dysfunction, and protein deposition on contact lens.[6,31,32] In 2 studies, the authors' conclusions did not address the use of acetylcysteine in the treatment of ocular silver nitrate burn or for superficial punctate keratitis.[33,34] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

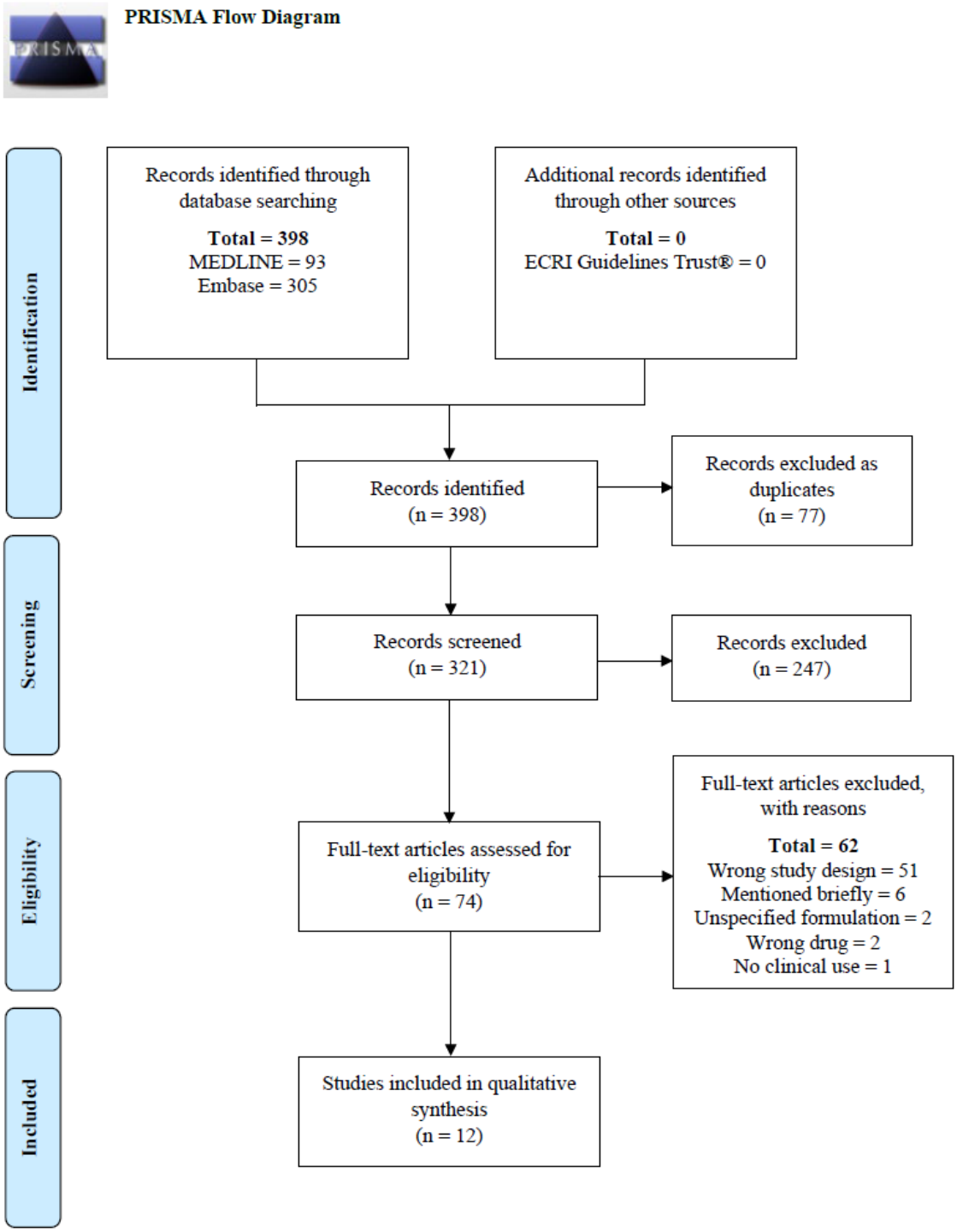
In addition to the 12 included studies, additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of acetylcysteine.

Acetylcysteine is available as an FDA-approved product for oral, inhalation, and intravenous administration and is approved for all of the nominated indications, except for the treatment of dry eyes via an ophthalmic solution. As of July 9, 2021, acetylcysteine is not listed on the FDA Drug Shortages list.[35] However, acetylcysteine oral and inhalation solutions are both on the American Society of Health-System Pharmacists (ASHP) Current Drug Shortages list (first posted June 28, 2011 and updated June 1, 2021).[36] The reason provided for this shortage is that the vials are on back order with the manufacturers.[36]

Meibomian gland dysfunction (MGD) is a chronic condition of the eye most frequently caused by the obstruction of the meibomian gland due to "hyperkeratinization of the duct epithelium and pluggin with a solidified secretion."[6] This obstruction causes the accumulation of meibum which leads to inflammation and bacterial colonization.[6] This can result in a compromised tear film lipid layer which can lead to dry eyes.[6] Treatment includes warm compresses, lid hygiene, artificial tears, topical and systemic antibiotics, topical steroids, and topical anti-inflammatory agents.[6,25] *N*-acetyl-cysteine (NAC) is "an acetylated derivative of the natural amino acid L-cysteine."[6] NAC has several properties that allow it to be successfully used as an ophthalmic medication, including serving as a mucolytic, anticollagenolytic, and antioxidant as well as influencing several inflammatory pathways.[6,25] As a result, NAC has been used successfully in ophthalmology to "to treat corneal diseases, such as keratoconjunctivitis sicca, filamentary keratitis, corneal mucous plaques, and alkali burned corneas. Improved wound healing has been shown in experimentally induced corneal ulcers by using NAC."[6,25]

One study that was not included due to being a case series from Austria described a polymer that was introduced to the European market in 2014, chitosan-*N*-acetylcysteine, which has a 24 hour ocular surface retention time, which would "achieve longer ocular surface residence times," requiring less frequent instillations.[37] This polymer, also known as Lacrimera®, is classified as a medical device and is "approved for short-term alleviation of dry eye symptoms."[32,37]

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[27,29,30,34]	4
Observational[26,33]	2
Experimental[6,24,25,28,31,32]	6

Table 4. Number of studies by country

Country	**Number of Studies**
Austria[32]	1
Mexico[28]	1
Turkey[6,25]	2
UK[24]	1
US[27,29-31,33,34]	6
Multiple Countries • UK and US[26]	1
	Total US[a]: 7 Total Non-US Countries[a]: 6

[a]Study [26] counted in both US and non-US total.

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Keratoconjunctivitis sicca					
Absolon and Brown, 1968, UK[24]	Double-blind cross-over trial	30 Patients with keratoconjunctivitis sicca (4%, range 43-77 y)	Patients started with either: • Artificial tears (17) • Acetylcysteine (13) Patients then crossed over to: • Artificial tears (12) • Acetylcysteine (15)	Resolution of symptoms	"The conclusion that treatment with the mucolytic agent acetylcysteine on the whole produced significantly better objective results than treatment with artificial tears, emphasizes the importance of the role of mucus in the production of the corneal changes."
Fraunfelder et al, 1977, UK and US[26]	–	17 Patients who were part of a keratoconjunctivitis sicca study who also had corneal mucus plaques (23.5%, range 27-75 y)	• Acetylcysteine (not reported) "Because of variation in frequency and severity of corneal mucus plaques, the use of topical acetylcysteine was individualized."	Occurrence of corneal mucus plaques	"The condition may be symptomatic but can be controlled and prevented in most cases by topical ocular application of 10% acetylcysteine."
Messner and Leibowitz, 1971, US[27]	Report of a case	1 Patient with presenting with filamentary keratitis (0%, 65 y)	Patient received 1 intervention in each eye: • Acetylcysteine (1) • Hydrophilic contact lens, chloramphenicol drops, normal saline drops (1)	Conjunctiva injection, presence of mucoid deposits/secretions	"Acetylcysteine therapy prevented mucus accumulation and resulted in clearing of conjunctival injection, relief of foreign body sensation and blepharospasm, and a marked improvement in visual acuity. A therapeutic trial with a hydrophilic contact lens also produced considerable symptomatic relief. However, this device was not as effective as acetylcysteine administration either in alleviating symptoms or preventing mucus accumulation."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 2: Dry eye or dry eye syndrome					
Ralph et al, 1975, US[29]	–	12 Patients requiring continuous ocular perfusion for a variety of disease states including Stevens-Johnson syndrome, keratoconjunctivitis sicca, alkali burns, ocular pemphigoid, persistent epithelial defect following penetrating keratoplasty for chronic herpes simplex keratitis, low level of tear production and undergoing keratoplasty for aphakic bullous keratopathy (58.3%, mean 47.2 y)	Continuous ocular perfusion of a variety of solutions including: • Balanced salt solution (BSS; 2) • Combinations of BSS, artificial tear solution, and acetylcysteine (5) • Homologous serum (5) • Autologous serum (1) • Homologous plasma (1) 1 Patient received 3 different solutions, resulting in the 12 patients using pump perfusion on 14 occasions Each case also had gentamicin sulfate to achieve a final concentration of 0.003%	Patient outcome and satisfaction	"At the present time, the indications for the use of such a mobile ocular perfusion system are most convincing in those severe dry-eye patients undergoing surgical procedures such as keratoplasty or reconstruction of the lids and conjunctival fornices. Based on our experiences with complex cases of this nature, we suggest the use of continuous wetting of the ocular surfaces during at least the first two postoperative months."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Schmidl et al, 2017, Austria[32]	Controlled, randomized double-blind clinical investigation	38 Patients with dry eye syndrome (DES) • Cohort 1 (29%, median 36 y) • Cohort 2 (23%, median 24 y)	• Cohort 1: Chitosan-*N*-acetylcysteine (C-NAC) drops in 1 eye and placebo in the other eye (21) • Cohort 2: C-NAC administered twice daily in 1 eye and once daily in the other (17)	Tear film thickness (TFT)	"In conclusion, this study has demonstrated that C-NAC eye drops are safe and effective when applied once or twice per day for 5 consecutive days in patients with DES. Treatment with C-NAC led to a significant increase in TFT over time compared with placebo and lasted for 24 h after a single instillation. Moreover, the clinical improvement of C-NAC treatment was confirmed by improved OSDI [Ocular Surface Disease Index] scores, reduced incidence of corneal damage, and reduced frequency of symptoms of ocular discomfort and conjunctival redness in Cohort II after 5 days of C-NAC treatment. As current DES therapies often require multiple daily instillations, C-NAC could provide a viable option for the treatment of DES and could improve the quality of life of the vast number of people suffering with DES. A multicentric phase 4 study investigating the efficacy and safety of C-NAC during long-term use is currently ongoing to further elucidate the clinical effectiveness of C-NAC."
Indication 3: Meibomian gland dysfunction					
Akyol-Salman et al, 2010, Turkey[6]	Prospective, randomized study	20 Patients presenting with meibomian gland dysfunction (MGD) • N-acetylcysteine (NAC; 60%, mean 40.60 y ± 12.54) • Preservative-free artificial tears (60%, mean 40.90 y ± 21.86)	• NAC (10) • Preservative-free artificial tears (10)	Ocular symptoms, fluorescein break-up time values, Schirmer scores	"The results of this prospective randomized clinical trial suggest that topical administration of NAC is effective and well tolerated in patients with MGD. The demonstrated efficacy of NAC in the patients is presumably based on its mucolytic, antioxidant, and anti-inflammatory properties. These findings should be further evaluated in large-scale, controlled clinical trials."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Akyol-Salman et al, 2012, Turkey[25]	Prospective, randomized study	20 Patients presenting with MGD • NAC (50%, mean 43.60 y ± 17.86) • Betamethasone-sulfacetamide sodium (60%, mean 39.80 y ± 21.61)	• NAC (10) • Betamethasone-sulfacetamide sodium suspension (10)	Ocular symptoms, fluorescein break-up time values, Schirmer scores, intraocular pressure	"The results of this prospective randomised clinical trial suggest that topical NAC and betamethasone-sulfacetamide sodium, a topical steroid-antibiotic combination, are effective and well-tolerated topical therapeutic agents in the treatment of sign and symptoms of MGD. When used with concomitant eyelid hygiene, topical administration of NAC appears to be as effective as betamethasone-sulfacetamide sodium, a topical steroid-antibiotic combination therapy, in patients with MGD."
Indication 4: Keratitis mucosa					
Shaw and Gasset, 1974, US[30]	Case report	1 Patient presenting with diffuse keratitis (0%, 30 y)	Initial therapy with a variety of wetting and lubricating agents and a brief trial of NAC. Then fitted with hydrophilic contact lens. Due to diffuse abnormal mucus obscuring contact lens, patient also received NAC 20% diluted in half with Neosporin-polymyxin ophthalmic solution for 2 weeks. Over next 3 months, strength was reduced to 3% and dilution switched to artificial tears (1)	Visual acuity	"Conventional treatment with artificial tears and acetylcysteine failed to relieve pain or increase visual acuity. However, combination therapy using Griffin soft contact lenses and acetylcysteine yielded highly satisfactory results."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 5: Ocular silver nitrate burn					
Laughrea et al, 1985, US[34]	Case reports	2 Patients receiving treatment for ocular burn after receiving silver nitrate for treatment of superior limbic keratoconjunctivitis (0%, range 22-56 y)	• Bilateral patching, acetylcysteine, prednisolone phosphate, scopolamine, and chloramphenicol ointment (1) • Patching, prednisolone acetate, acetylcysteine, chloramphenicol, and atropine (1)	Healing	"The use of solid silver nitrate should be prohibited around the eye."
Indication 6: Primary pterygia					
Parra et al, 2019, Mexico[28]	Prospective, observational, and descriptive study	15 Eyes* with primary pterygia (gender and age not specified) *Number of patients was not reported	• Oral NAC (5 eyes) • Topical NAC (5 eyes) • Control (5 eyes)	Histopathologic characteristics including vascular density, stromal elastosis, stromal fibrosis, inflammation, changes in epithelium	"This study shows that NAC ocular instillation reduces the inflammatory, epithelial hyperplasia and elastotic changes, that could influence the development and eventual recurrence of pterygium and may be useful in the therapeutic management of this disease."
Indication 7: Protein deposition on contact lenses					
Kruh et al, 2015, US[31]	Prospective, nonrandomized clinical trial	9 Patients with a prior history of either Boston Keratoprosthesis type I and/or trichiasis from Stevens-Johnson syndrome, and required full-time contact lens wear (55.6%, range 18-86 y)	All patients served as their own control: • Control for 1 month (9) • NAC for 2 months (9)	Protein deposition	"We believe that this pilot study establishes the efficacy of topical NAC use, although we feel that a larger population controlled clinical trial with a longer follow-up period is necessary to corroborate our results."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 8: Superficial punctate keratitis					
Cosar et al, 2003, US[33]	–	22 eyes of 16 Patients with pediatric keratoplasties • Topical cyclosporine (CsA; 50%, mean 15.3 months ± 7.9) • Control (50%, mean 68.8 months ± 15.5)	• CsA (6) • Control (10) 4 Eyes developed superficial punctate keratitis (SPK) and 4 eyes developed SPK with filamentary keratopathy that responded to artificial tears, mechanical removal of filaments, and 10% acetylcysteine	Treatment of SPK	"We conclude that topical 2% CsA treatment in pediatric keratoplasties is safe and efficacious in the postoperative care of these challenging patients."

Abbreviations: "–", not mentioned; BSS, balanced salt solution; C-NAC, chitosan-*N*-acetylcysteine; DES, dry eye syndrome; MGD, meibomian gland dysfunction; NAC, *N*-acetylcysteine; TFT, tear film thickness.

[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Keratoconjunctivitis sicca[26,27]	Apply 1-4 times per day	10%	–	Ophthalmic	–
	Apply 1 drop every 2 hours while awake	20%	Solution		At least 5 days
Dry eye[29]	2-8 mL per day	1-2%	Solution	Ophthalmic	2-993 days
Keratitis mucosa[30]	Apply 1-2 drops every 20-30 minutes	3-10%	Solution	Ophthalmic	At least 3.5 months
	Apply 4 times per day				
Ocular silver nitrate burn[34]	Apply 4 times per day	20%	–	Ophthalmic	–
Protein deposition on contact lens[31]	Apply 1 drop 4 times per day	20%	–	Ophthalmic	2 months
Superficial punctate keratitis[33]	–	10%	–	Ophthalmic	–

Abbreviations: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Keratoconjunctivitis sicca[24,26]	Apply 1-4 times per day	10%	–	Ophthalmic	–
	Apply every 2 hours per eye	20%	Solution		2 months
Meibomian gland dysfunction[6,25]	Apply 4 times per day	5%	–	Ophthalmic	1 month
Dry eye syndrome[32]	Apply 1-2 times per day	0.10%	Drops	Ophthalmic	5 days
Primary pterygia[28]	–	10%	–	Ophthalmic	–

Abbreviations: "–", 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 ninety-nine SMEs were contacted for interviews; 63 agreed to be interviewed, and 136 declined or failed to respond to the interview request. Five SMEs discussed acetylcysteine. The 5 SMEs were medical doctors who were specialized and/or were board-certified in ophthalmology, working in academic medical institutiond and outpatient practice. The SMEs had been in practice for 13 to 32 years.

Acetylcysteine has been used for patients with severe dry eyes and aqueous tear deficiency that have developed filamentary keratitis or filamentary keratopathy, a painful disorder where collections of mucin and debris become attached to the surface of the cornea. Acetylcysteine drops can be applied to the eyes for several weeks and it helps to break down the mucoid discharge in the eye. However, despite the effectiveness and low cost as compared to alternative agents, acetylcysteine is an unpopular therapy due to it having a foul odor. One SME stated that, despite seeing a lot of very severe dry eyes, they have probably only prescribed acetylcysteine 10 times in their 32 years of practice, instead opting for other treatment options. Another SME said that they have not found a pharmacy that will compound acetylcysteine, but due to the availability of other options this has not been a concern in their practice, stating, “I don’t feel like I need it, I feel like I can manage my patients without that one.” However, despite infrequent use, one SME stated that “what acetylcysteine does isn’t an expected action from anything that’s commercially available,” adding that “we’d like to have it around…it’s a small market, but I think it’s a real need because filaments are really difficult.”

One SME mentioned that acetylcysteine is occasionally used as an ophthalmic product for treating burns but had never seen it used.

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 16 for characteristics of the facilities that the participants represented). A prequestionnaire was also distributed to participants (refer to Tables 16-19 for results of the prequestionnaire).

While a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtained 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 1 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 5-minute gown and glove. If we don't have somebody in the IV [intravenous] room, if you're doing <797> right, it's 5 minutes. It's 4 minutes to tube it. It's 3 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 pressor 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 with 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 stated that, while they do not obtain a lot of products from outsourcing facilities, "when we do purchase from 503Bs, 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 coronavirus disease 2019 (COVID-19) pandemic has also impacted the operations of hospitals, as noted by 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 cleanroom 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 [more] 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 midsize 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 the 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 within 1 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 used. However, the products used 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 9 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 also said 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 Health-System Pharmacists] and the FDA allow." 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 from bulk . . . especially for the pediatric patient population." However, another participant from a children's hospital said that they have never needed to use an outsourcing facility for preservative-free products. 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 cleanroom 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 are 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. 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 [that] are doing the nonsterile 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 nonsterile 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 <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 noted that it "is a challenge for anybody who has 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 which 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 . . . 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 3 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 to 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 2400, either one, compounder. Then we send it up to [*sic*] 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 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 "[t]raditionally, we've found 503Bs 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 503Bs where we've had agreements for certain products to take it off our plate, and then lo 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 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.

Among respondents, 0 (0%) used acetylcysteine.

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 16 for respondent characteristics. Among respondents, 35 (81% of 43 total respondents) used outsourcing facilities to obtain drug products, 4 (9%) did not use 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 drug shortages (refer to Table 17).

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 18 for the categories of products obtained from outsourcing facilities.

One respondent (0.9% of 108 responses, where respondents were allowed to select multiple drug products) obtained acetylcysteine from a 503B outsourcing facility (refer to Table 19).

Table 11. Characteristics of survey respondents

No survey respondents provided this information

Table 12. Compounded products prescribed or administered

Condition	Responses, n (N=1)
Acetylcysteine	0
Bupivacaine hydrochloride	0
Clonidine hydrochloride	0
Tetracaine hydrochloride	0
Triamcinolone acetonide	1
Tropicamide	0
None of the above	0

Table 13. Conditions for which acetylcysteine prescribed or administered

No survey respondents provided this information

Table 14. Reasons for using compounded acetylcysteine

No survey respondents provided this information

Table 15. Use of non-patient-specific compounded acetylcysteine

No survey respondents provided this information

Table 16. 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=39)**
< 50	4
50-99	3
100-199	1
200-299	4
300-399	5
400-599	3
> 600	19

[a]Respondents allowed to select multiple facilities.
[b]Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, and oncology.

Table 17. 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 on-site compounding facility	1
On-site compounding facility not equipped to compound all necessary products	19
Other[b]	8

[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 using outsourcing facilities.

Table 18. 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 19. 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

Acetylcysteine was nominated for inclusion on the 503B Bulks List as a 5 to 15% ophthalmic solution to treat dry eyes caused by meibomian gland dysfunction and as a 10% and 20% inhalation solution and IV solution to treat acetaminophen overdose, administration of anesthesia for procedure, amyloidosis, atelectasis due to mucous obstruction, bronchiectasis, bronchopulmonary disease, chronic bronchitis, chronic disease of the respiratory system, chronic obstructive pulmonary disease (COPD), diagnostic procedure on lower respiratory tract, distal intestinal obstruction syndrome, emphysema, giant papillary conjunctivitis (GPC), mucolysis, nephrotoxicity prophylaxis, pulmonary complications of cystic fibrosis, respiratory complications of surgical procedures, and tracheostomy care. Acetylcysteine is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Canada, Hong King, Latvia, Namibia, New Zealand, Saudi Arabia, the UK, and the US.

From the literature review, acetylcysteine was used to treat keratoconjunctivitis sicca, dry eyes, meibomian gland dysfunction, keratitis mucosa, ocular silver nitrate burn, primary pterygia, protein deposition on contact lenses, and superficial punctate keratitis. Acetylcysteine was used as an ophthalmic solution in concentrations ranging from 0.1-20% administered every 30 minutes to 1-2 times a day. The authors concluded that the use of acetylcysteine for the treatment of dry eye syndrome, meibomian gland dysfunction, and protein deposition on contact lens requires further studies. The authors' conclusions did not address the use of acetylcysteine in the treatment of ocular silver nitrate burn or for superficial punctate keratitis.

From the interviews, while acetylcysteine is effective for the treatment of filamentary keratitis, it is used infrequently due to the foul odor and availability of other commercially available options. However, filamentary keratitis can be difficult to treat, and acetylcysteine has a unique mechanism compared to the commercially available options, so it is important to maintain access to the compounded product. The SMEs did not see a need for this product to be stocked in-office, stating that if this therapy was to be used they would write a patient-specific prescription.

From the survey responses, 0 out of 1 respondent used acetylcysteine. From the prequestionnaire, 1 respondent obtained acetylcysteine from a 503B outsourcing facility.

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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 August 7, 2020
- Date last searched: August 10, 2020
- Limits: Humans (search hedge); English language
- Number of results: 93

1	acetylcysteine/	13186
2	acetylcystein$.tw.	12525
3	acetilcistein$.tw.	7
4	acetilcystein$.tw.	5
5	asetilsistein$.tw.	1
6	asetylsistein$.tw.	0
7	asetilsystein$.tw.	0
8	acetyl cystein$.tw.	3786
9	acetil cistein$.tw.	1
10	acetil cystein$.tw.	2
11	asetil sistein$.tw.	0
12	asetyl sistein$.tw.	0
13	asetil systein$.tw.	0
14	acetyl l cystein$.tw.	4396
15	acetil l cistein$.tw.	0
16	acetil l cystein$.tw.	2
17	asetil l sistein$.tw.	0
18	asetyl l sistein$.tw.	0
19	asetil l systein$.tw.	0
20	or/1-19	23953

21	administration, ophthalmic/	1228
22	intraocular$.tw.	66379
23	ocular$.tw.	125765
24	ophthalm$.tw.	102564
25	exp ophthalmic solutions/	14870
26	(eye adj2 drop?).tw.	6380
27	eyedrop?.tw.	2164
28	exp dry eye syndromes/	19072
29	(dry$ adj2 eye$).tw.	8475
30	((sicca or xerosis) adj2 (conjunctiv$ or cornea$ or keratoconjunctiv$ or keratit$)).tw.	1550
31	((sicca or sjo?gren$) adj2 syndrom$).tw.	16079
32	xerophthalm$.tw.	922
33	or/21-32	282513
34	and/20,33	147
35	exp animals/ not humans/	4724133
36	34 not 35	100
37	limit 36 to english language	93

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: August 10, 2020
- Limits: Humans (search hedge); English language
- Number of results: 305

1	‘acetylcysteine'/de	36648
2	‘acetylcystein*':ti,ab,tn	16540
3	‘acetilcistein*':ti,ab,tn	6
4	‘acetilcystein*':ti,ab,tn	16
5	‘asetilsistein*':ti,ab,tn	2
6	‘asetylsistein*':ti,ab,tn	1
7	‘asetilsystein*':ti,ab,tn	0
8	‘acetyl cystein*':ti,ab,tn	5214
9	‘acetil cistein*':ti,ab,tn	5
10	‘acetil cystein*':ti,ab,tn	8
11	‘asetil sistein*':ti,ab,tn	2
12	‘asetyl sistein*':ti,ab,tn	0
13	‘asetil systein*':ti,ab,tn	0
14	‘acetyl l cystein*':ti,ab,tn	4996
15	‘acetil l cistein*':ti,ab,tn	0
16	‘acetil l cystein*':ti,ab,tn	1
17	‘asetil l sistein*':ti,ab,tn	0
18	‘asetyl l sistein*':ti,ab,tn	0
19	‘asetil l systein*':ti,ab,tn	0
20	#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 OR #18 OR #19	40401
21	‘intraocular drug administration'/exp	11859
22	‘conjunctival drug administration'/de	458

23	‘intraocular*':ti,ab	85573
24	‘ocular*':ti,ab	172374
25	‘ophthalm*':ti,ab	160776
26	‘eye drops'/de	14564
27	(eye NEAR/2 drop$):ti,ab	9703
28	‘eyedrop$':ti,ab	2832
29	‘dry eye'/de	15587
30	‘sjoegren syndrome'/de	24085
31	‘keratoconjunctivitis sicca'/de	2459
32	‘xerophthalmia'/de	2232
33	(dry* NEAR/2 eye*):ti,ab	12402
34	((sicca OR xerosis) NEAR/2 (conjunctiv* OR cornea* OR keratoconjunctiv* OR keratit*)):ti,ab	2063
35	((sicca OR sjo$gren*) NEAR/2 syndrom*):ti,ab	22906
36	‘xerophthalm*':ti,ab	1292
37	#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	406631
38	#20 AND #37	437
39	[animals]/lim NOT [humans]/lim	6072261
40	#38 NOT #39	349
41	#38 NOT #39 AND [english]/lim	305

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. Which of the following drugs do you prescribe or administer to your patients? (please check all that apply)
    - o Acetylcysteine
    - o Bupivacaine hydrochloride
    - o Clonidine hydrochloride
    - o Tetracaine hydrochloride
    - o Triamcinolone acetonide
    - o Tropicamide
    - o None of the above
3. I prescribe or administer compounded [substance from question 2] in combination with other active pharmaceutical ingredients as a multi-ingredient product.
    - o Yes, please explain _____
    - o No
4. Do you prescribe or administer [substance from question 2] by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Local/perineural injection
    - o Intracameral injection
    - o Intraocular injection
    - o Ophthalmic solution, suspension, or gel
    - o Other (please describe) _____
    - o None of the above
5. I prescribe or administer [substance from question 2] for the following conditions or diseases:
    - o Anesthesia for ophthalmic procedures
    - o Dilation for mydriasis induction
    - o Dry eye caused by meibomian gland dysfunction
    - o Peribulbar or retrobulbar block
    - o Other, please explain _____
    - o None of the above
6. I prescribe or administer [substance from question 2] with my patients as the following;
    - o FDA-approved drug product
    - o Compounded drug product

- Over-the-counter drug product
- Other (please explain) _____

7. I used compounded [substance from question 2] because: (please 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 [substance from question 2]
   - Other (please explain) _____
8. Do you stock non-patient-specific compounded [substance from question 2] at your practice?
   - Yes
   - No
   - I'm not sure
9. I obtain compounded [substance from question 2] from the following: (please 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) _____
10. What is your practice setting? (please check all that apply)
    - Physician office/private practice
    - Outpatient clinic
    - Hospital/health system
    - Academic medical center
    - Emergency room
    - Operating room
    - Other (please describe) _____
11. What degree do you hold? (please 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 specialty(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-facilities.
    - 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 on-site compounding facility
    - On-site compounding facility not equipped to compound all necessary products
    - Other, please explain _____
5. Please select the type(s) of products obtained from an outsourcing facility.
    - Nonsterile products
    - Sterile products
6. Please select the category(ies) of products obtained from an outsourcing facility.
    - Cardioplegic solutions
    - Dermatologic preparations
    - Dialysate solutions

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

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

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

Appendix 3. Survey distribution to professional associations

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

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