Summary Report

Bupivacaine hydrochloride

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

ADC	Automated dispensing cabinet
API	Active Pharmaceutical Ingredient
ASHP	America Society of Health-System Pharmacists
ED	Emergency department
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HCl	Hydrochloride
IV	Intravenous
IRB	Institutional Review Board
OR	Operating room
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 (US) Food and Drug Administration (FDA) in its evaluation of the use of bupivacaine hydrochloride (bupivacaine HCl; UNII code: 7TQO7W3VT8), 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 bupivacaine HCl 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 bupivacaine HCl 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 bupivacaine HCl 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

Bupivacaine HCl was nominated for inclusion on the 503B Bulks List by Fagron, Pentec Health, the Outsourcing Facilities Association (OFA), the Specialty Sterile Pharmaceutical Society (SSPS), and US Compounding Pharmacy.

Bupivacaine HCl was nominated for cataract anesthesia and pain control as a 0.25% to 0.75% ocular or ophthalmic product. In addition, bupivacaine HCl as both preserved and preservative-free products was nominated as an injectable 0.4 to 35 mg/mL solution to be administered via epidural, caudal, intravenous (IV), nerve block/perineural, infiltration, and intrathecal injection for analgesia and anesthesia. Bupivacaine HCl was nominated for use in combination with fentanyl or other narcotics; however, no specific formulations were provided.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of bupivacaine HCl.[6-26]

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

- Intraocular injections are invasive and can increase the risk of complications; topical bupivacaine application can provide a less invasive alternative for cataract surgery.
- Practitioners often prescribe doses that require higher strengths or concentrations than those available in FDA-approved products or use in combinations with other medications.
- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patient need for dosage form or strength, including greater concentration, that is not available commercially.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Manufacturer backorder.
- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes, and/or final product containers for administration,
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical size batch for outsourcing facilities; a single vessel compounded from bulk API is safer and more efficient than unmanageable amounts of small vials.

- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100% potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- To utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of bupivacaine HCl products in the 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 bupivacaine HCl; name variations of bupivacaine HCl 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 bupivacaine HCl. 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: bupivacaine HCl and ophthalmic administration or form (refer to Appendix 1 for full search strategies). A literature review was not conducted for perineural, epidural, caudal, or intrathecal administration due to the availability of FDA-approved products for these routes. A literature review was not conducted for IV administration because an SME who specialized in anesthesiology stated that bupivacaine HCl was unlikely to be administered via this route. Results were limited to human studies in English language. Searches were conducted November 10, 2020. In addition, the ECRI Guidelines Trust® repository was searched November 10, 2020 for clinical practice guidelines that recommended the use of bupivacaine HCl 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 bupivacaine HCl 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 bupivacaine HCl was used as: an FDA-approved product in the nominated dosage form, ROA, or combination; a dosage form, ROA, or combination that was not nominated; an unspecified dosage form or ROA; used for an indication that was not nominated; used for a non-clinical use; or mentioned briefly as a previous failed treatment. Studies in which bupivacaine HCl 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 bupivacaine HCl; setting; total number of patients; number of patients who received bupivacaine HCl; patient population; indication for use of bupivacaine HCl; dosage form and strength; dose; ROA; frequency and duration of therapy; use of bupivacaine HCl in a combination product; use and formulation of bupivacaine HCl in a compounded product; use of bupivacaine HCl compared to FDA-approved drugs or other treatments; outcome measures; and authors' conclusions. One reviewer extracted data from the included studies, and a second reviewer checked the data extraction.

Interviews

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances bupivacaine HCl 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 bupivacaine HCl. 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 bupivacaine HCl 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

- Bupivacaine HCl is available as an FDA-approved product in the nominated dosage form and ROA.
- Bupivacaine HCl is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for bupivacaine HCl.
- Bupivacaine HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, the EU, Hong Kong, Ireland, 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]
Bupivacaine HCl	0.25-1.33%	Injectable, Liposomal injectable	Injection, Spinal	Prescription	Approved prior to 01/01/1982
Bupivacaine HCl, Epinephrine[c]	0.25-0.75%	Injectable	Injection	Prescription	Approved prior to 01/01/1982

[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.
[c]Salt form either not provided or "epinephrine bitartrate."

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]
Bupivacaine HCl	0.125-1.33%	Dispersion, Powder for suspension, Solution, Solution for injection	Block/infiltration, Caudal, Epidural, Intramuscular, Intrathecal, Intravenous, Percutaneous infiltration, Perineural, Peripheral nerve block, Retrobulbar, Subcutaneous	Abu Dhabi	Active	–
				Australia	S4 – Prescription only medicine	01/10/1991
				Belgium	Medical prescription	11/15/1970
				Canada	Ethical	12/31/1994
				EU	Authorized	09/17/2020
				Hong Kong	Prescription only	01/13/1992
				Ireland	Prescription-only non-renewable	04/02/1987
				Latvia	Prescription	04/03/2006
				Namibia	–	06/28/1976
				New Zealand	Prescription	02/22/1972
				Saudi Arabia	Prescription	–
				UK	Prescription-only medication	03/09/2000
	0.5%	Solution	Topical	Saudi Arabia	Prescription	–
Bupivacaine HCl, Epinephrine	0.25-0.5%	Solution, Solution for injection	Block/infiltration, Caudal, Dental, Epidural, Infiltration,	Abu Dhabi	Active	–
				Australia	S4 – Prescription only medicine	07/31/1991

			Intramuscular, Percutaneous infiltration, Nerve block, Perineural, Peripheral nerve block, Subcutaneous	Belgium	Medical prescription	1/23/1970
				Canada	Ethical	12/31/1994
				Hong Kong	Prescription only	06/24/1997
				Ireland	Prescription-only non-renewable	05/31/1988
				New Zealand	Prescription	12/31/1969
				UK	Prescription-only medication	03/15/1991
Bupivacaine HCl, Fentanyl	0.1-0.125%	Solution	Epidural	Australia	S8 – Controlled drug	05/23/1994
				New Zealand	Controlled	10/25/2001
				UK	Prescription-only medication	09/14/2011
Bupivacaine, Meloxicam	60-400 mg	Prolonged release wound solution	Surgical site	EU	Authorized	07/23/2020

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 656 references; 2 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 489 titles and abstracts were screened. After screening, the full text of 188 articles was reviewed. Finally, 16 studies were included. One hundred seventy-two studies were excluded for the following reasons: wrong study design (110 studies); dosage form, ROA, or combination not nominated (47); FDA-approved formulation (8); unspecified ROA or formulation (3); bupivacaine HCl not used clinically (2); unable to obtain (1); and wrong substance (1).

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

Characteristics of included studies

The 16 included studies were published between 1995 and 2016. There were 12 experimental studies, 2 observational studies, and 2 descriptive studies. The 16 studies were conducted in the following countries: Egypt, Finland, France, Germany, UK, and US.

A total of 1503 patients participated in the 16 included studies. The number of patients in each study ranged from 16 to 278.

Outcome measures differed among the included studies, and included ability to repair multiple lacerations, mean aqueous humor level, need for intravenous (IV) sedation, operating conditions, pain score, patient comfort and satisfaction, postoperative sedation, preoperative intraocular pressure, surgical outcome, and visual disturbances.

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

Use of bupivacaine HCl

Sixteen patients received bupivacaine HCl as a one-time soluble ophthalmic insert in doses ranging between 0.5 mg and 1 mg. Three hundred fifty-nine patients received bupivacaine via topical administration to the eye in strengths ranging between 0.5% and 0.75%. Duration of treatment ranged from once to 24 hours.

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

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

In 10 studies, the authors' concluding statement recommended the use of topical anesthesia containing bupivacaine HCl for ophthalmic procedures.[27-36] In 1 study, the authors concluded that applying bupivacaine-soaked sponges in the conjunctival fornices for deep topical fornix nerve block (DTFNBA) was effective and reliable.[37] In 1 study, the authors concluded that bupivacaine 1 mg is an efficient and safe dose when administered via soluble ophthalmic insert, but the use of hyaluronic acid requires further studies.[38] In 1 study, the authors' concluding statement was that lidocaine gel was a better topical anesthetic in comparison to bupivacaine and benoxinate drops, but that bupivacaine drops were effective for providing deep topical anesthesia.[39] In 1 study, the authors concluded that a single application of topical lidocaine gel with intracameral anesthesia provided similar analgesia to multiple applications of combined topical anesthesia with intracameral

anesthesia.[40] In 1 study, the authors' conclusion was that paraocular anesthesia gave better analgesia, but topical anesthesia containing bupivacaine provided acceptable analgesia.[41] In 1 study, the authors' concluding statement was that limited and supervised use of topical anesthetics is recommended for pain control following photorefractive keratectomy, but that bupivacaine was inferior to tetracaine.[42] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 16 included studies, additional references were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and availability of bupivacaine HCl.

One study that was excluded from the review for wrong study design commented that "it has been well documented that patients prefer topical anaesthesia to retrobulbar or peribulbar anaesthesia, mainly due to the avoidance of the injection involved."[43] The author added that patients exhibit fewer intraoperative and postoperative complications with topical anesthesia and that "adjunction of topical pre-operative treatment with intracameral lignocaine has been reported to be safe and effective; in particular it improves patient co-operation and reduces discomfort caused by tissue manipulation for pharcoemulsification."[43] A 1995 review by Bloomberg and Pelican listed the potential (albeit rare) complications of retrobulbar and periocular anesthesia, including total loss of vision, loss of the eye, and death.[44] Besides safety, Bloomberg and Pelican listed other benefits of topical anesthesia, such as "more rapid return of vision, no loss of ocular motility, and elimination of the risk of ptosis and bruising."[44] The authors of 2 of the included studies concluded that topical anesthesia is a safer option compared to retrobulbar anesthesia "because it eliminates many of the potential problems with injection anesthesia."[35,36]

Despite the lack of FDA approval for IV administration of bupivacaine HCl, the literature search did not review the clinical use of bupivacaine HCl due to reports of practitioners avoiding use due to increased concerns of local anesthetic-induced cardiac toxicity with this route. An editorial written in 1979 commented that "the relative toxicity of etidocaine and presumably bupivacaine is disproportionately high (twofold) when administered intravenously, compared with absorption from injection sites, because these drugs have high lipid solubility. At 1 mcg/mL bupivacaine and etidocaine are 95 per cent bound in plasma, with a rapid decrease in the percentage bound as the plasma concentration exceeds 4-5 mcg/ml, thereby increasing the fraction of free base available to cross the nerve membrane. If cardiac toxicities of bupivacaine and etidocaine are similar to that of dibucaine, a steep dose-response curve would be anticipated, with marked cardiovascular depression occurring at plasma levels only slightly above that for CNS [central nervous system] toxicity."[45] There were not many studies done with IV bupivacaine HCl in human patients, although the author of a 1971 study looking at the administration of IV bupivacaine HCl to volunteers and the clearance of the drug said that "acute toxicity studies on animals with bupivacaine, lignocaine, and mepivacaine have shown that bupivacaine is 4 times as toxic as the other 2 compounds, and this ratio has been taken as a general guide of the relative toxicities of these compounds."[46] However, the volunteers were able to tolerate high bupivacaine HCl plasma levels that were described as "among the highest levels recorded in conscious patients to date."[46] The volunteers did exhibit symptoms but "subjective signs of toxicity were mild;" there were no convulsions "but muscular rigidity of the body occurred and lasted for about 10 minutes."[46] As a result, the authors suggested that a potential explanation for discrepancies between animal and human toxicity data might be "the differences in plasma protein binding of these compounds," and noted that in animal studies, the dose given is typically "so large that relative differences in plasma protein binding of the drugs will probably be swamped and the

values obtained will probably reflect more the intrinsic toxicities of the compounds."[46] In 1989, a randomized double-blind study took place to compare IV infusions of bupivacaine HCl with ropivacaine to assess CNS and cardiovascular toxicity.[47] While the authors found no difference regarding cardiovascular changes, "there was a clear difference between the drugs in regards to their ability to produce mild symptoms of CNS toxicity," with 7 out of the 12 subjects able to tolerate the full dose of ropivacaine at 150 mg, while only 1 subject was able to tolerate the same dose of bupivacaine.[47] The mean tolerated IV doses for ropivacaine and bupivacaine were 124 mg ± 38 and 99 mg ± 30, respectively.[47] In this study, ropivacaine was found to cause fewer CNS symptoms, and while "both drugs caused evidence of depression of conductivity and contractility, these appeared at a lower dosage and lower plasma concentrations with bupivacaine than with ropivacaine."[47] As a result, the authors concluded that "ropivacaine is a less toxic compound than bupivacaine," although they added that more clinical trials were needed in humans to determine the relative therapeutic ratios.[47]

A 2009 systematic review looked at the adverse events associated with IV regional anesthesia (IVRA), also referred to as "Bier block."[48] Through their review of the literature, the authors found 64 cases where the patient exhibited complications after receiving IVRA with either lidocaine, prilocaine, or bupivacaine.[48] Major complications that were related to systemic local anesthetic toxicity and occurred in 39 patients included seizures, cardiac arrest, and death, along with the following "unusual" reactions: "talked excitably or incomprehensibly, or had unusual behavior" (considered to be preictal); curare-like reaction ("ptosis and partial loss of muscle power"); acute aphasia for 20 hours; and temporary bilateral blindness.[48] The author noted that the lowest dose of bupivacaine associated with adverse events was 1.3 mg/kg for a seizure and 1.6 mg/kg for cardiac arrest.[48] They also said that cardiac arrests and deaths were only reported for lidocaine and bupivacaine, not prilocaine.[48] Major complications that were not related to systemic local anesthetic toxicity included nerve damage and compartment syndrome, although for the latter, "inadvertent use of hypertonic saline either used for dilution of the local anesthetic or as a chaser (fluid injected after the local anesthetic) was implicated in 5 of those cases."[48] Minor complications associated with IVRA included skin discoloration or widespread petechiae; hypertension; painful injection; and thrombophlebitis.[48] However, the author said that the "major complications related to local anesthetic toxicity may occur during tourniquet inflation or after tourniquet deflation," although "a tourniquet time of 30 minutes does not always prevent systemic local anesthetic toxicity after tourniquet deflation."[48] Furthermore, the author suggested keeping the dose of local anesthetic under the lower limit of serious toxicity and added that there were 3 other local anesthetics that "seem less toxic than the others when accidentally injected intravascularly: articaine, prilocaine, and chloroprocaine," at least in the appropriate patient populations.[48] The authors concluded that "IVRA is associated with a low incidence of complications and can therefore be considered a safe anesthetic technique. Using a dose of local anesthetic less than that known to induce a seizure or methemoglobinemia might help in decreasing the occurrence of serious adverse events associated with IVRA."[48]

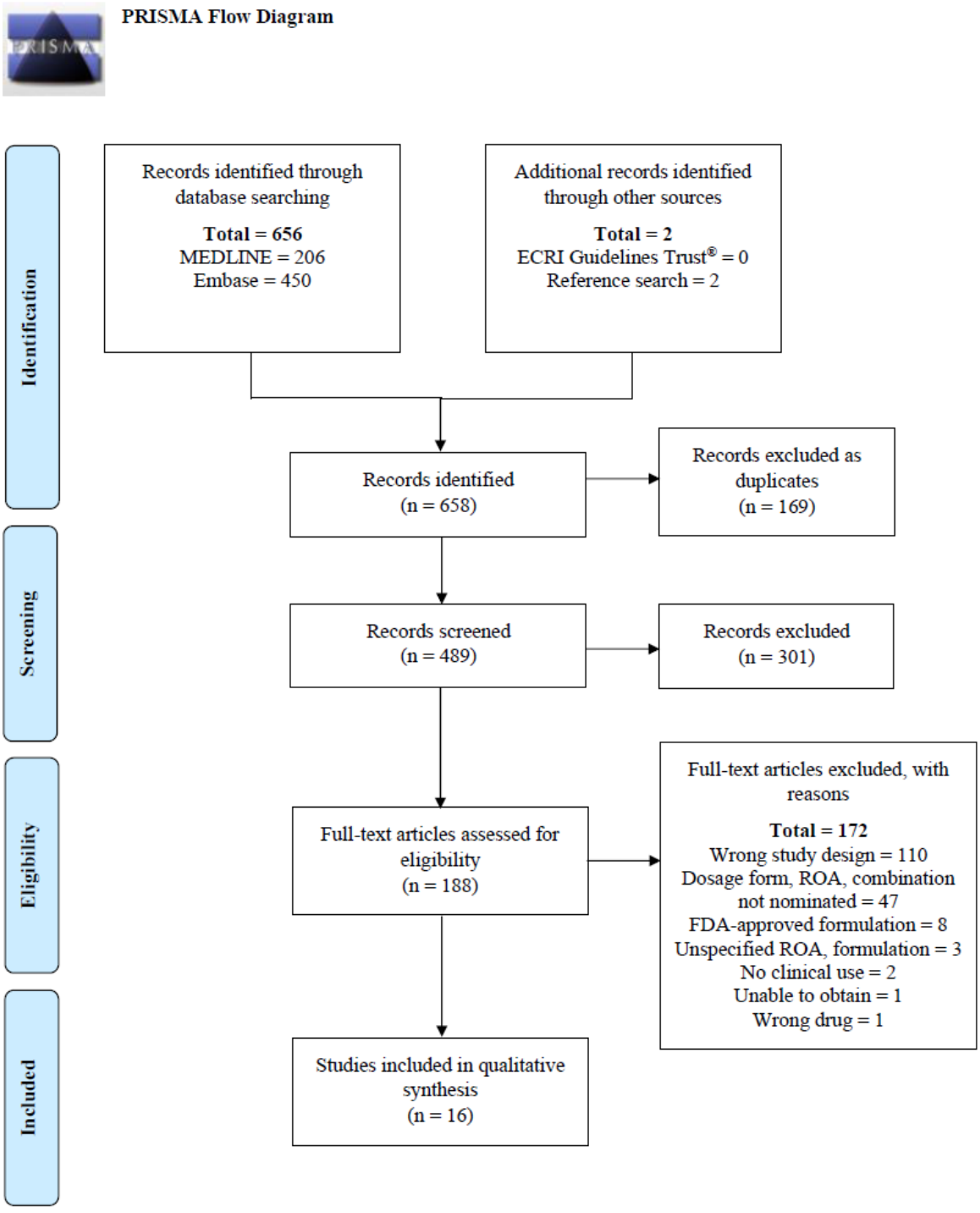
Inadvertent intravascular administration of bupivacaine HCl is still a concern with intrathecal and epidural ROA – something that practitioners need to keep in mind and a justification for using a test dose containing epinephrine and monitoring heart rate to confirm appropriate needle placement.[49] Additionally, there have been reports of accidentally administering bupivacaine HCl via IV instead of via epidural route, as seen in the Karaca et al 2002 case report.[50] The patient developed adverse symptoms including ringing in the ears, palpitations, dizziness, and sinus tachycardia.[50] Fortunately, the nurse was present when the patient started to exhibit symptoms, and the patient was transferred safely to the ICU and eventually discharged without requiring treatment.[50] However, the author noted that "the striking feature of accidental i.v. bupivacaine is the great difficulty in resuscitating the

patient. In convulsant dosages, local anesthetics cause increases in blood pressure, heart rate and cardiac output by stimulating the autonomic control centres in the brainstem; however, in our patient, the low concentration of the bupivacaine produced only a sinus tachycardia."[50]

However, local anesthetic systemic toxicity can still occur in other ROA besides IV. In a review from 1995, the authors describe the risks of toxic systemic reactions of long-acting local anesthetics bupivacaine HCl and etidocaine for dental procedures.[51] The authors commented that regarding use in neural blockade, bupivacaine HCl has been determined to be 4 times as potent as lidocaine and 2 times as potent as etidocaine.[51] In this review, the authors provided a recommended maximum bupivacaine HCl dose of 1.25 mg/kg; the maximum dose for lidocaine and etidocaine were 5.0 mg/kg and 8.0 mg/kg, respectively.[51] They concluded that long-acting local anesthetics "can be safely [used] if proper patient selection, injection technique, and maximum dose guidelines are adhered to."[51]

Both the FDA Drug Shortages list and the America Society of Health-System Pharmacists (ASHP) Current Drug Shortages list include bupivacaine HCl products.[52,53] The FDA list included bupivacaine HCl injection (first posted February 20, 2018) and bupivacaine HCl and epinephrine injection (February 20, 2018).[52] The ASHP list included bupivacaine HCl injection (November 16, 2011) and bupivacaine HCl and epinephrine injection (September 2, 2016).[53] The reasons provided for these shortages included discontinuation of manufacturing, increased demand for the product, manufacturing delay, and "other."[52,53]

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[27,28]	2
Observational[29,32]	2
Experimental[30,31,33-42]	12

Table 4. Number of studies by country

Country	**Number of Studies**
Egypt[37,39]	2
Finland[41]	1
France[38]	1
Germany[40]	1
UK[30,31,42]	3
US[27-29,32-36]	8
	Total US: 8 Total Non-US Countries: 8

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: Ophthalmic anesthesia					
Ahmed et al, 2002, US[35]	Prospective, randomized study	40 Outpatients having elective combined surgery without a history of intraocular surgery or procedures involving the conjunctiva (gender and age not specified)	• Preoperative anesthesia with topical bupivacaine (20) • Retrobulbar block with lidocaine, bupivacaine, and hyaluronidase (20)	Operating conditions, patient comfort, surgical outcome	"We found comparable efficacy with both anesthesia techniques. Topical anesthesia is safer than retrobulbar anesthesia for combined phacotrabeculectomy as it eliminates many of the potential problems of injection anesthesia."
Bloomberg, 1998, US[27]	–	275 Patients scheduled for anterior segment surgery under topical anesthesia using the Bloomberg Ophthalmic Ring (gender and age not specified)	• Preoperative instillation of bupivacaine with lidocaine and epinephrine, followed by eye drops of diclofenac, bupivacaine, phenylephrine, and tropicamide. Intraoperative bupivacaine and lidocaine eye drops before placing the Bloomberg Ophthalmic Ring which has been saturated in a mixture of bupivacaine and lidocaine (275)	Patient satisfaction	"Patient reactions to the use of topical anesthesia have been positive. Patients who have had one cataract extraction with periocular anesthesia and one eye done under topical anesthesia, have indicated great satisfaction with topical anesthesia. The key advantages expressed by patients who have had both types of anesthesia are that immediately after the surgery they have no 'droopy lid,' no 'wooden head' sensation of numbness, rapid return of vision, and no double vision."
Eggleston, 1996, US[28]	Case report	1 Patient with a traumatic injury to the left eye with resultant rupture of pre-existing radial and transverse incisions (100%, age not specified)	• Sedation with midazolam and propofol, periorbital block with lidocaine. Eye drops of tetracaine and bupivacaine were used as needed (1)	Ability to repair multiple lacerations	"I present this case to emphasize that, with the properly motivated patient and with proper use of an orbital block, topical anesthetic medication and intraocular anesthetics can be used to repair multiple lacerations of the globe. This prevented the possibility of the patient developing severe respiratory problems from a possible aspiration process."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Eissa et al, 2016, Egypt[37]	Double-blinded, randomized, prospective controlled study	107 Patients scheduled for implantable collamer lens (ICL) procedure • Topical (45.3%, mean 63.66 y ± 4.25) • Deep topical fornix nerve block (DTFNBA; 42.6%, mean 68.532 y ± 6.725)	• Topical anesthesia with tetracaine drops (53) • DTFNBA with bupivacaine-soaked sponges applied deep in the conjunctival fornices (54)	Pain scores and patient-reported level of discomfort	"Placing the anesthetic in the fornix makes the DTFNBA more effective and reliable block."
Kansal et al, 2002, US[29]	Prospective study	278 Patients undergoing either day-surgery or inpatient trabeculectomy, phacotrabeculectomy, or aqueous shunt surgery Blitz group • Trabeculectomy (44.9%, mean 69 y) • Phacotrabeculectomy (26.7%, mean 76 y) • Aqueous shunt (46.7%, mean 69 y) Retrobulbar group • Trabeculectomy (34.7%, mean 71 y) • Phacotrabeculectomy (40.7%, mean 74 y) • Aqueous shunt (55.5%, mean 70 y)	Blitz group: • Bupivacaine or mepivacaine eye drops followed by intraocular lidocaine and anterior sub-Tenon's anesthesia, also known as Blitz anesthesia (139) Retrobulbar group: • Topical tetracaine followed by retrobulbar injection (139)	Operative and postoperative pain scores, postoperative sedation, amount of intravenous sedation used, and preoperative intraocular pressure	"Blitz anesthesia offers a reasonable alternative to retrobulbar anesthesia for trabeculectomy, phacotrabeculectomy, and aqueous shunt surgery."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Lagnado et al, 2003, UK[30]	–	40 Patients having phacoemulsification for senile cataract under topical anesthesia without sedation (gender not specified, range 49-90 y)	• Topical bupivacaine 3 drops (18) • Topical bupivacaine 6 drops (22)	Mean aqueous humor level, pain scores, and visual disturbances	"A 3-drop regimen of bupivacaine 0.75% in the half hour before cataract surgery penetrated the eye as effectively as 6 drops in the 1 hour before surgery and provided good analgesia for phacoemulsification. Bupivacaine 0.75% penetrated the eye increasingly effectively with increasing age."
Maclean et al, 1997, UK[31]	Prospective study	50 Patients scheduled for cataract surgery under local anesthesia (30%, range 42-91 y)	• Peribulbar injection (25) • Topical bupivacaine plus lignocaine injection (25)	Pain score	"The modified topical technique provided satisfactory patient comfort during cataract surgery; it was comparable to the comfort achieved using peribulbar injections. The speed and ease of administering topical anesthesia coupled with the rapid visual recovery after surgery makes this method a suitable and safe choice for day-case phacoemulsification cataract surgery."
Mahe et al, 2005, France[38]	Prospective, double-blind, cross-over, randomized study	16 Healthy subjects not undergoing any procedures (55%, mean 28.5 y ± 4.8)	4 Soluble ophthalmic inserts: • Bupivacaine 1 mg and hyaluronic acid (16) • Bupivacaine 0.5 mg and hyaluronic acid (16) • Bupivacaine 1 mg (16) • Placebo (16)	Complete and satisfactory anesthesia	"Bupivacaine 1 mg seems to be the efficient and safe dose. The value of hyaluronic acid as a corneal hydration agent and used in association with bupivacaine will be the subject of further studies."
Novak et al, 1995, US[32]	–	20 Patients who underwent phacoemulsification under topical anesthesia (gender and age not specified)	3 Topical anesthesias: • Bupivacaine (17) • Lidocaine (2) • Proparacaine (1)	Patient-reported intraoperative and postoperative comfort	"Topical anesthesia is not appropriate for every patient or for every surgeon. But this study shows that the transition from injection anesthesia to topical anesthesia can be made safely for the patient and relatively easily and atraumatically for the surgeon."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Patel et al, 1996, US[33]	Prospective, randomized study	138 Patients undergoing elective cataract extraction and intraocular lens implantation (gender and age not specified)	• Topical bupivacaine and IV midazolam and fentanyl (69) • IV methohexital followed by retrobulbar block (69)	Pain score	"Topical anesthesia can be used safely for cataract extraction. The degree of patient discomfort is only marginally higher during administration of the anesthesia and postoperatively. However, surgical training and patient preparation are the keys to the safe use of topical anesthesia."
Patel et al, 1998, US[34]	Prospective, randomized study	90 Patients having elective cataract extraction and intraocular lens implantation (gender and age not specified)	• Topical bupivacaine and IV midazolam and fentanyl (45) • IV methohexital followed by retrobulbar block (45)	Pain score	"Cataract surgery was safely performed by a surgeon converting to topical anesthesia. After a distinct learning curve, the procedure was performed with minimal patient discomfort. Surgical training and patient preparation are the key to safe use of topical anesthesia."
Soliman et al, 2004, Egypt[39]	Prospective, randomized study	90 Patients scheduled for routine cataract extraction • Lidocaine (40%, mean 65.3 y ± 7.2) • Bupivacaine (44%, mean 64.2 y ± 6.1) • Benoxinate (48%, mean 63.9 y ± 7.1)	• Lidocaine gel (30) • Bupivacaine eyedrops (30) • Benoxinate eyedrops (30)	Pain score	"Lidocaine gel was a better topical anesthetic agent than bupivacaine and benoxinate drops. Bupivacaine drops were effective in providing deep topical anesthesia."
Thill et al, 2005, Germany[40]	Randomized, double-blind study	39 Patients undergoing cataract surgery with topical anesthesia • Bupivacaine (38%, mean 71.5 y ± 10.4) • Lidocaine (50%, mean 71.1 y ± 9.1)	• 1 Drop each of topical bupivacaine, diclofenac, and oxybuprocaine (21) • Topical lidocaine gel (18)	Pain scores	"A single application of lidocaine gel 2% combined with intracameral anesthesia provides at least as good analgesia than multiple administration of combined topical anesthesia supplemented with intracameral anesthesia and is equally safe."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Uusitalo et al, 1999, Finland[41]	–	245 patients scheduled for cataract extraction • Topical group (30.1%, mean 72.2 y) • Paraocular group (35%, mean 71.3 y)	• Topical group with bupivacaine drops (136 eyes) • Paraocular group (163 eyes)	Pain score, patient-reported satisfaction	"Paraocular anesthesia gave better analgesia than topical, but topical anesthesia provided acceptable analgesia during surgery and showed that intraocular procedures can be performed without akinesia. The surgeon converting to topical anesthesia may expect slight difficulty in 40% of cases and more severe difficulty in 7%. Surgically related complications were similar with both methods."
Verma et al, 1997, UK[42]	Prospective, double-masked trial	38 Patients undergoing photorefractive keratectomy (PRK; 26.3%, mean 40.18 y)	• Tetracaine eye drops (19) • Bupivacaine eye drops (19)	Pain score	"Contrary to our expectation, the longer acting anaesthetic, bupivacaine, was inferior to tetracaine. Limited and supervised use of topical anaesthetics is recommended in controlling pain following photorefractive keratectomy."
Zabriskie et al, 2002, US[36]	Prospective study	36 Out-patients undergoing elective primary trabeculectomy without previous surgery involving the conjunctiva (gender and age not specified)	• Preoperative anesthesia with topical bupivacaine (20) • Retrobulbar block with lidocaine, bupivacaine, and hyaluronidase (20)	Operating conditions, patient comfort, surgical outcome	"In summary, both topical and retrobulbar anesthesia provide equally efficacious optimal operative conditions for the surgeon and excellent pain control for the patient. However, topical anesthesia is a safer alternative to retrobulbar anesthesia for glaucoma surgery because it eliminates many of the potential problems with injection anesthesia."

Abbreviations: –, not provided; DTFNBA, deep topical fornix nerve block; IV, intravenous; PRK, photorefractive keratectomy.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Ophthalmic anesthesia[27-29,32-36]	4-8 drops	0.75%	Eye drops, Solution	Topical	Once, preoperatively
	2-4 drops every 5-10 minutes				20-25 minutes before surgery
	As needed				As needed

Table 7. Dosage by indication – non-US countries

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Ophthalmic anesthesia[30,31,37-42]	0.5-1 mg	–	Soluble ophthalmic insert	Topical	Once
	3-4 drops	0.50-0.75%	Solution		Once – 4 applications
	1-6 drop every 3-10 minutes				12-60 minutes
	Every 30 minutes during waking hours, maximum of 40 drops				24 hours

Abbreviation: –, not provided.

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No compounded products from reported 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. Eight SMEs discussed bupivacaine HCl; these included 7 medical doctors and 1 nurse practitioner. The SMEs specialized and/or were board-certified in anesthesiology, ophthalmology, and oncology, working in academic medical institutions, outpatient practice, and community hospital. The SMEs had been in practice for 12 to 35 years. Additional information was collected as part of the Expanded Information Initiative, referred to as Phase 3, project in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

One SME discussed the use of bupivacaine HCl in anesthesiology. The ROA will determine the local anesthetic used. Bupivacaine HCl is the only anesthetic that is FDA-approved for administration into the spine and is the agent used when a spinal anesthetic is needed. The SME uses hyperbaric bupivacaine. For epidural administration, the SME uses either lidocaine or ropivacaine. While bupivacaine is occasionally used, it is typically only when testing an epidural or providing a "top-up." Ropivacaine and mepivacaine are preferred when performing peripheral nerve blocks and the choice between the 2 will depend on the length of block required. The SME stated that occasionally bupivacaine HCl is used, but commented that they have not used it in 15 years because a large volume is required and there is a risk of the patient developing toxicity. The SME mentioned that due to the availability of ropivacaine there is no reason to use bupivacaine for peripheral nerve blocks due to the risk of cardiac toxicity.

Six SMEs discussed the use of bupivacaine HCl in ophthalmology. Anesthesia for cataract surgery can be applied either topically to the eye or as a retrobulbar injection "where you're injecting the medication behind the eye." Tetracaine, proparacaine, or lidocaine would typically be used as a topical anesthetic and bupivacaine would be used as a retrobulbar injection. The retrobulbar injection will "numb the eye completely." Retrobulbar blocks were performed in cataract surgery, but "we don't do much now for cataract surgery." This can be attributed to the shortened duration of cataract surgery "so you don't need the anesthesia." Additionally, "most cataract surgeons like to have the patient be able to move their eyes a little bit because they can improve the access to the cataract at the time of surgery." Retrobulbar injections are also associated with several risks and complications including "diplopia, [as] there's risk of hitting the muscle, risk of even globe perforation, injecting into the retina, even blindness is a potential risk. Or even if you inject it into the optic nerve, you can get even death." One SME stated that retrobulbar blocks for cataract surgery are deviating from the standard of care commenting that "I would testify against somebody for doing retrobulbar blocks." Now "the trend has been to be going more topical." After the administration of topical drops, a small incision is made into the eye and an intraocular injection of "a small amount and it numbs the structures inside the eye, but it doesn't numb the muscles" can be made at the time of surgery. This injection is still considered a topical application but allows for "ultra-local" anesthesia to be administered.

One SME was not familiar with using bupivacaine topically. Two SMEs commented that the longer duration of action associated with bupivacaine would be problematic for cataract surgery. Historically, ophthalmologists would "patch the eye after surgery," which keeps the eye closed. The patch would be removed "the next morning when the anesthetic has worn off." However, with the use of topical anesthetics, the eye does not need to be covered allowing the patient to "see right after a cataract surgery." If a longer-acting anesthetic was used "you'd have the problem that the patient wouldn't feel something in the eye, so they could get a corneal abrasion, the eye would dry out because their blink reflex would go down. You wouldn't want something long lasting for that kind of surgery."

While retrobulbar blocks are not used in cataract surgery "they are still done for many retinal procedures." A retrobulbar or peribulbar block is used frequently prior to retinal procedures in surgeries that will last longer than the anesthesia that a lidocaine block would provide with 1 SME commenting that "bupivacaine is important in our surgery." Three SMEs stated that they typically use a mixture of bupivacaine and lidocaine to provide both a short acting and long acting anesthetic.

One SME commented on the use of bupivacaine for intrathecal pain pumps. The preferred agent for intrathecal pumps is bupivacaine; use of ropivacaine is limited due to being more expensive. Local anesthetics are typically usually used in conjunction with other substances in intrathecal pumps, unless the patient has an allergy to the drug class. A patient that is started on an intrathecal pump "has failed all conservative therapy." Patients are typically trialed on a medication prior to a pump being inserted to ensure that the dose is appropriate, and the patient is not experiencing any side effects. During the trial, the patient is kept in the hospital and "you mirror the implantation of the pump" by administering the drug via a catheter into the intrathecal space. After the trial, the pump can be implanted and started at the dose determined during the trial. When performing sympathetic blocks, the SME prefers ropivacaine because bupivacaine is associated with more decreases in blood pressure and there is already a risk of patients becoming hypotensive with these types of blocks.

One SME has never used bupivacaine.

As part of Phase 3, 3 nominators provided additional information regarding the products that will be compounded using bupivacaine HCl.

Bupivacaine HCl will be compounded as a 0.25% ophthalmic injection for use as cataract anesthesia and pain control applied once daily for more than 1 day. This product is used by practitioners as a non-patient-specific compounded product in inpatient settings, operating rooms, outpatient clinics, and physician offices. This compounded product is needed because bupivacaine alone or in combination with lidocaine creates successful pain management and anesthesia for cataract surgery. The addition of topical bupivacaine can provide a less-invasive alternative for cataract surgery.

Bupivacaine HCl will be compounded as a 31.25 mg/mL solution for intrathecal injection for use as spinal anesthesia as a continuous infusion implanted intrathecal pump. This product is used by practitioners as a non-patient-specific compounded product in acute care facilities, outpatient clinics, and physician offices. This compounded product is needed because it will be a higher strength than the FDA-approved product and will be preservative-free. The concentration needed for filling implanted intrathecal pumps is 30 to 35 mg/mL and the highest concentration from an FDA-approved product is 7.5 mg/mL. Additionally, the FDA-approved products contain methylparaben and preservatives, which are contraindicated for intrathecal use. Another nominator stated that this compounded product is also needed because bupivacaine HCl is often used in combination with other medications.

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 obtain varied from less than 1% to the majority of compounded products used at 1 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, such as emergency departments (EDs) and operating rooms (ORs). 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 (ADCs) 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 ADC, 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 [OR], minimize manipulations as much as possible." Similarly in the ED, 1 participant stated they prefer ready-to-use products for some floor-stock items, like vasopressor infusions, to prevent compounding from occurring on the floor. 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 the decision of which products to purchase from an outsourcing facility was focused on the use and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, such as the ED and OR, 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 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, such as 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 1 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 1 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; therefore, they 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 encouraging 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 labeled adequately, including in OR and other settings in which procedures are performed. USP <795> and <797> are applicable in OR 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, it was expected that they had similar needs regarding the concentrations and volumes of products utilized. 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, 1 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. [If] 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, 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 [emergency room] 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 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 … 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 affected equally and unable to provide assistance. However, 1 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. According to 1 participant, as long as buyers are familiar with regulations and know what to look for 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, 1 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. 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, 1 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 cannot, 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; 1 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. Lidocaine-epinephrine-tetracaine (LET) gel used 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 availability of commercial 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 1 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 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 1 participant observed, "When you need it, it's an emergency" and another noted that it "is a challenge for anybody who has the cyclophosphamide-induced hemorrhagic cystitis." As a result, 1 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 [treatment]. 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. 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 infrequent. 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 1 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 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 using 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, "Traditionally, 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 1 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 using 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).

Among respondents, 0 (0%) used bupivacaine HCl.

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). Amongst 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 responses) 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 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).

Eight respondents (7% of 108 responses, where respondents were allowed to select multiple drug products) obtained bupivacaine HCl 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

Product	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 bupivacaine HCl prescribed or administered

No survey respondents provided this information

Table 14. Reasons for using compounded bupivacaine HCl

No survey respondents provided this information

Table 15. Use of non-patient-specific compounded bupivacaine HCl

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 onsite compounding facility	1
Onsite 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, and 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

Bupivacaine HCl was nominated for inclusion on the 503B Bulks List as an ophthalmic product for use as anesthesia and for pain control during cataract surgery, and as a preserved and preservative-free product for epidural, caudal, IV, nerve block/perineural, infiltration, and intrathecal injection for use as analgesia and anesthesia. Bupivacaine HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, the EU, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, the UK, and the US.

From the literature review, 16 studies were included. Bupivacaine HCl was used as an ophthalmic solution and insert for use as ophthalmic analgesia. In the majority of the included studies, the authors recommended the use of topical anesthesia containing bupivacaine HCl for ophthalmic procedures.

From the interviews, newer surgical techniques have eliminated the need for retrobulbar injections with bupivacaine HCl prior to cataract surgery; however, these injections are still used prior to retinal procedures. When used prior to a retinal procedure, bupivacaine is used commonly in combination with lidocaine to provide both a short-acting and long-acting anesthetic. None of the SMEs had experience using bupivacaine as a topical preparation, and, due to the length of cataract surgery, there would be concerns with use of a longer-acting anesthetic. Bupivacaine is the only anesthetic that is FDA-approved for spinal administration. Bupivacaine is also the anesthetic of choice for use in implantable pain pumps. Bupivacaine is not used frequently as a peripheral nerve block or a sympathetic nerve block due to the risk of side effects and toxicity.

As part of phase 3, 3 nominators provided additional information regarding the products that will be compounded using bupivacaine HCl. Bupivacaine HCl will be compounded as a 0.25% ophthalmic injection for use as cataract anesthesia and pain control, and as a 31.25 mg/mL solution for intrathecal injection for use as spinal anesthesia as a continuous infusion implanted intrathecal pump.

From the survey responses, 0 out of 1 respondent used bupivacaine HCl. From the prequestionnaire, 8 respondents obtained bupivacaine HCl 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 November 9, 2020
- Date last searched: November 10, 2020
- Limits: Humans (search hedge); English language
- Number of results: 206

1	bupivacaine/	12,021
2	bipuvacain$.tw.	3
3	bupicain$.tw.	2
4	bupiv#cain$.tw.	13,404
5	buv#cain$.tw.	1
6	or/1-5	16,930
7	administration, ophthalmic/	1273
8	exp ophthalmic solutions/	14,976
9	ocular$.tw.	127,848
10	ophthalm$.tw.	104,384
11	((conjunctiva$ or eye?) adj3 (appl$ or drop? or infus$ or instill$ or topical$)).tw.	10,345
12	eyedrop?.tw.	2186
13	or/7-12	224,226
14	and/6,13	268
15	exp animals/ not humans/	4,754,125
16	14 not 15	244
17	limit 16 to english language	206

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: November 10, 2020
- Limits: Humans (search hedge); English language
- Number of results: 450

1	‘bupivacaine’/de	37,971
2	‘bipuvacain*’:ti,ab,tn	9
3	‘bipuvicain*’:ti,ab,tn	1
4	‘bupacain*’:ti,ab,tn	0
5	‘bupicain*’:ti,ab,tn	13
6	‘bupivacain*’:ti,ab,tn	19,064
7	‘bupivicain*’:ti,ab,tn	482
8	‘buvacain*’:ti,ab,tn	4
9	‘buvicain*’:ti,ab,tn	1
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	39,331
11	‘intraocular drug administration’/de	4302
12	‘conjunctival drug administration’/de	479
13	‘eye drops’/de	14,904
14	‘ocular*’:ti,ab	175,806
15	‘ophthalm*’:ti,ab	163,698
16	((conjunctiva* OR eye$) NEAR/3 (appl* OR drop$ OR infus* OR instill* OR topical*)):ti,ab	15,405
17	‘eyedrop$’:ti,ab	3592
18	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	322,443
19	#10 AND #18	574
20	[animals]/lim NOT [humans]/lim	6,117,471
21	#19 NOT #20	537
22	#19 NOT #20 AND [english]/lim	450

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)
    - ○ Acetylcysteine
    - ○ Bupivacaine hydrochloride
    - ○ Clonidine hydrochloride
    - ○ Tetracaine hydrochloride
    - ○ Triamcinolone acetonide
    - ○ Tropicamide
    - ○ 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.
    - ○ Yes, please explain _____
    - ○ 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)
    a. Local/perineural injection
    b. Intracameral injection
    c. Intraocular injection
    d. Ophthalmic solution, suspension, or gel
    e. Other (please describe) _____
    f. None of the above
5. I prescribe or administer [substance from question 2] for the following conditions or diseases:
    a. Anesthesia for ophthalmic procedures
    b. Dilation for mydriasis induction
    c. Dry eye caused by meibomian gland dysfunction
    d. Peribulbar or retrobulbar block
    e. Other, please explain _____
    f. None of the above
6. I prescribe or administer [substance from question 2] with my patients as the following;
    a. FDA-approved drug product
    b. Compounded drug product

c. Over-the-counter drug product
d. 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 onsite compounding facility
    - Onsite compounding facility not equipped to compound all necessary products
    - Other, please explain _____
5. Please select the type(s) of products obtained from an outsourcing facility.
    - Nonsterile products
    - Sterile products
6. Please select the category(ies) of products obtained from an outsourcing facility.
    - Cardioplegic solutions
    - Dermatologic preparations
    - Dialysate solutions

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

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

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

Appendix 3. Survey distribution to professional associations

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

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