

# Summary Report

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## Lidocaine hydrochloride

### Prepared for:

US Food and Drug Administration

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

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## Frequently Used Abbreviations

ADC	Automated dispensing cabinet
API	Active Pharmaceutical Ingredient
ED	Emergency department
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HCl	Hydrochloride
IRB	Institutional Review Board
IV	Intravenous
OTC	Over-the-counter
OR	Operating room
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

## INTRODUCTION

This report was created to assist the United States Food and Drug Administration (FDA) in its evaluation of the use of lidocaine hydrochloride (lidocaine HCl; UNII code: V13007Z41A and EC2CNF7XFP), 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 lidocaine 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 lidocaine HCl has been used historically and currently.<sup>1-3</sup> 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.<sup>1,4,5</sup> Rather, the aim was to summarize the available evidence on the use of lidocaine 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

Lidocaine HCl was nominated for inclusion on the 503B Bulks List by Pentec Health, the Specialty Sterile Pharmaceutical Society (SSPS), US Compounding Pharmacy, Pine Pharmaceuticals, and the Outsourcing Facilities Association (OFA). Lidocaine HCl was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Lidocaine HCl was nominated for use via multiple dosage forms and routes of administration (ROA) including nasal solutions, ophthalmic solutions, ophthalmic ointments, ophthalmic gels, topical creams, patches, topical ointments, topical lotions, topical gels, topical jellies, topical sprays, topical solutions, rectal creams, rectal gels, epidural injections, intra-articular injections, intracardiac injections, intradermal injections, intramuscular injections, intrathecal injections, intravenous (IV) injections, infiltration injections, perineural injections, subcutaneous injections, and dental injections. The concentration used will depend on the dosage form and ROA and can range from 0.25% to 30%; there is also a need for preservative-free preparations to be compounded. While the medical condition in which lidocaine HCl will be used to treat may not be known, lidocaine HCl is FDA-approved for a variety of indications and is generally used as a local anesthetic in various procedures, treatment of severe pain, status epilepticus, stomatitis, certain cardiac arrhythmias, and symptoms of topical fungal infections.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of lidocaine HCl.<sup>6-23</sup>

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

- Practitioners often prescribe doses that require higher strengths or concentrations than those available in FDA-approved products or use in combinations with other medications.
- 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.
- Practitioner or facility need for different strength or form, or ready-to-use packaging.
- Manufacturer backorder.
- There are no 505-approved drugs intended for topical administration containing this API.
- 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.
- Lidocaine is the predominant local anesthetic agent used in the US.
- There are multiple combination products compounded using lidocaine that are not available from any FDA-approved manufacturer; using FDA-approved products as a starting material would increase the number of manipulations needed, which in turns increases risk of contamination and resultant risk to the patient.
- All FDA-approved products contain preservatives and ,therefore, a bulk drug substance is necessary to make a preservative-free product.

## **METHODOLOGY**

### *Background information*

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

lidocaine 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*

Lidocaine HCl is a component of an FDA-approved product. The nominated products did not differ substantially from the commercially available product. Therefore, a systematic literature review was not conducted.

### *Interviews*

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances lidocaine 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 lidocaine 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 lidocaine 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 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*

- Lidocaine HCl is available as an FDA-approved product in the nominated dosage form and ROA.
- Lidocaine HCl is available as an OTC product in the US via topical, transdermal, and rectal ROA.
- There is a current United States Pharmacopeia (USP) monograph for lidocaine HCl.
- Lidocaine HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, and the UK.

Table 1. Currently approved products – US<sup>a</sup>

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date <sup>b</sup>
Lidocaine HCl	0.008-1%	Injectable	Injection, Spinal	Prescription	Approved prior to 1/01/1982
	0.5 mg	System	Intradermal	Prescription	8/16/2007
	3.5%	Gel	Ophthalmic	Prescription	10/07/2008
	2%	Solution	Oral	Prescription	11/18/1982
	1.8-5%	Jelly, Ointment, Patch, Solution	Topical	Prescription	Approved prior to 1/01/1982

Abbreviations: HCl, hydrochloride.

<sup>a</sup>Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

<sup>b</sup>If multiple approval dates and/or multiple strengths, the earliest date is provided.

Table 2. Currently approved products – select non-US countries and regions<sup>a</sup>

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date <sup>b</sup>
Lidocaine HCl	0.4-20% 0.5 mg 21.3 g 10 mg/actuation	Cream, Gel, Liquid, Liquid spray, Lotion, Ointment, Oral topical solution, Oral viscous solution, Patch, Powder, Solution, Solution for injection, Spray, Spray solution, Topical spray	Buccal, Cutaneous, Dental, Epidural, Intra-articular, Intradermal, Injection, Intramuscular, Intrathecal, Intravenous, Local infiltration, Nerve block, Oral, Oromucosal, Perineural, Rectal, Subcutaneous, Spinal, Topical	Abu Dhabi	Active	–
				Australia	S2 – Pharmacy medicine, S4 – Prescription-only medicine	08/13/1991
				Belgium	Medical prescription	03/01/1962
				Canada	Ethical	12/31/1951
				Hong Kong	Pharmacy only <sup>c</sup> , Prescription only	01/23/1979
				Ireland	Prescription-only non-renewable	04/01/1980
				Latvia	Prescription	04/12/2000
				Namibia	–	06/08/1973
				New Zealand	Prescription, Pharmacy	12/31/1969
				Saudi Arabia	Prescription	–
UK	Prescription-only medication, Pharmacy <sup>c</sup>	11/25/1986				

Abbreviation: –, not provided.

<sup>a</sup>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.

<sup>b</sup>If multiple approval dates and/or multiple strengths, the earliest date is provided.

<sup>c</sup>Pharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

## *Results of literature review*

*No literature review was conducted.*

### Pharmacology and historical use

Additional references were found that provided information about the pharmacology and availability of lidocaine HCl.

Lidocaine HCl, also known as lignocaine, was first synthesized between 1943 and 1946.<sup>24</sup> In addition to being a local anesthetic, lidocaine has also been used as an adjunct to tracheal intubation during advanced airway management and as an antiarrhythmic agent.<sup>24</sup>

Both the FDA Drug Shortages list and the American Society of Health-System Pharmacists (ASHP) Current Drug Shortages list include lidocaine HCl products.<sup>25,26</sup> The FDA list included the lidocaine HCl and dextrose injection solution in premixed bags (first posted October 25, 2017), lidocaine HCl injection (February 22, 2012), and lidocaine HCl with epinephrine (February 22, 2012).<sup>25</sup> The ASHP list included the 5% lidocaine and 7.5% dextrose injection (August 3, 2016), lidocaine injection (June 23, 2015), and lidocaine with epinephrine injection (November 16, 2011).<sup>26</sup> The reasons provided for these shortages included: discontinuation of manufacturing, increased demand for the product, manufacturing delay, supply interruption of raw ingredients, and “other.”<sup>25,26</sup>

The ASHP website mentioned resolved shortages of 2% lidocaine HCl topical jelly (February 22, 2018 through May 21, 2019), lidocaine HCl and 5% dextrose injection (November 11, 2011 through May 26, 2016 and January 3, 2018 through September 6, 2018), and lidocaine topical 4% solution (September 8, 2014 through May 26, 2016 and February 7, 2017 through October 8, 2017).<sup>26</sup>

ASHP initiated the Standardize 4 Safety program to develop national standardized concentrations for IV medications in both pediatrics and adults.<sup>27,28</sup> For lidocaine, the concentration standards for continuous infusions is 4 mg/mL and 8 mg/mL for pediatric patients, and 8 mg/mL in adult patients, which are commercially available.<sup>27,28</sup> ASHP states there is the possibility of concentration and unit mismatch depending on the pharmacy or outsourcing facility label.<sup>27,28</sup>

Table 3. Types of studies

*No literature review was conducted*

Table 4. Number of studies by country

*No literature review was conducted*

Table 5. Summary of included studies

*No literature review was conducted*

Table 6. Dosage by indication – US

*No literature review was conducted*

Table 7. Dosage by indication – non-US countries

*No literature review was conducted*

Table 8. Number of studies by combination

	<b>Combination Formula<sup>a,b</sup></b>
Nominated	Lidocaine HCl 1%/Chamomile extract 2%/Fluocinolone acetonide 0.025%/Witch hazel 5% (topical)

<sup>a</sup>The nomination from Pine Pharmaceuticals includes several combination products that have been compounded using lidocaine HCl; however, it is unclear if Pine Pharmaceuticals intends to compound these combination products.

<sup>b</sup>The nomination from US Compounding Pharmacy indicates a need to compound lidocaine HCl in combination with other active pharmaceutical ingredients for ophthalmic use; however, the nomination does not provide the formulation of these combination products.

*No literature review was conducted*

Table 9. Compounded products – US

*No literature review was conducted*

Table 10. Compounded products – non-US countries

*No literature review was conducted*

## *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. Sixteen SMEs discussed lidocaine HCl. In addition, 3 SMEs that specialized in dermatology and anesthesiology were interviewed in year 1 for a total of 19 SMEs that discussed lidocaine HCl. These 19 SMEs included 11 medical doctors, 3 dentists, 2 nurse practitioners, 1 dental hygienist, 1 pharmacist, and 1 registered nurse. The SMEs specialized and/or were board-certified in allergy, anesthesiology, dentistry, dermatology, infectious disease, oncology, ophthalmology, pain management, and pediatrics; and were working in academic medical institutions, consulting, private practice, inpatient practice, and outpatient practice. The SMEs had been in practice for 1 to 57 years. Additional information was collected as part of the Expanded Information Initiative project, referred to as Phase 3, in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

Lidocaine is used by a variety of medical practitioners in multiple practice settings as a local anesthetic prior to a procedure. Since it is used prior to procedures, it makes sense for practitioners to keep a stock of lidocaine in their office.

In dentistry, topical numbing agents typically are used prior to a procedure to numb the area before the injection of a local anesthetic. However, there are challenges with using topical numbing agents because there is a risk of saliva washing them away causing the product to run down the back of the throat, which numbs the throat. Most of the SMEs use topical benzocaine when a topical numbing agent is needed due to its availability. One SME commented that they prefer Cetacaine<sup>®</sup> (benzocaine/tetracaine/butamben) stating, “It’s got a fast onset... lasts a lot longer than, say, the 20% topical benzocaine that’s commonly available just about everywhere.” Another SME commented that they have also soaked a gauze with lidocaine and applied that to the gum to numb the area. The SMEs did use lidocaine, either with or without epinephrine, as an infiltration injection, but this is a commercially available product.

There are several commercially available topical numbing agents that contain lidocaine for use in dentistry. There are 2 commercially available combination products that contain lidocaine and prilocaine: Oraqix<sup>®</sup> (gel) and EMLA<sup>®</sup> (cream). One SME stated that Oraqix<sup>®</sup> is commonly used in dental hygiene practice for patients “that are going to be having a gingival procedure and not requiring the use of a drill or cutting into the enamel.” One SME stated that this combination “is probably the most common one used for the gingival sulcus.” Oraqix<sup>®</sup> also has a thermoset gelling action that allows it “[to] stay in the place you put it,” which is especially useful if a vasoconstrictor is not used. EMLA<sup>®</sup> is not used as commonly in dentistry. One SME stated, “I’d say one in maybe 20 hygienists might have this in their office, used topically.” The SMEs did not routinely use either of these products, but 1 commented that they occasionally use it to numb skin prior to placing an IV line. Lidocaine is also available as DentiPatch<sup>®</sup>, a transoral delivery system that is used for palatal anesthesia. Palatal injections may be needed when conducting a dental procedure within the gum tissue, but are difficult to administer because “it actually goes in several millimeters and there’s just not a lot of tissue. There’s no fat there. So, you go in several millimeters with the needle, and it actually contacts the bone. It’s uncomfortable.” The DentiPatch<sup>®</sup> can help alleviate some of the discomfort associated with the injection or can replace the need for the injection.

Three SMEs that specialized in cataract surgery discussed the use of lidocaine. At the start of the procedure, a series of eye drops are administered, including an antibiotic, phenylephrine, a dilating drop, and a topical anesthetic to numb the cornea. The challenge with the administration of multiple drops is that the eye can only hold a small volume. When multiple drops are being used “you really need to wait 3 to 5 minutes between drops.” However, this is often not done in a busy preoperative area and there is a

risk of drops not staying in the eye or “just diluting each other out.” Additionally, there is an increased risk of toxicity to the eye due to preservatives. One SME stated that they use a compounded solution that contains an antibiotic, lidocaine, Mydracyl® (tropicamide), and a nonsteroidal anti-inflammatory drug (NSAID). This solution helps “allow for each drop to do its thing effectively without having to wait minutes before the second one is applied.” The SME continued, “It is nice to have it all compounded into one delivery.” However, 2 SMEs provide anesthesia using the gel formulation of lidocaine instead of the ophthalmic solution. After the eye is numb, an intraocular injection of preservative-free lidocaine with epinephrine, also known as Shugarcaine, is administered into the anterior chamber. This provides anesthesia as well as additional dilation. The SMEs obtain this from a compounding pharmacy. One SME who specialized in retina surgery uses a combination of bupivacaine and lidocaine as a retrobulbar block, which provides both a short- and long-acting anesthetic prior to procedures. However, this formulation is commercially available.

In anesthesia and pain management, the type and length of block needed will determine the anesthetic that is used. Lidocaine is used frequently in epidurals as a lidocaine/epinephrine combination product that provides a quick surgical block. It’s followed by boluses with either ropivacaine or bupivacaine that have a slower onset but provide a longer block. Bupivacaine is the only anesthetic that is FDA-approved for spinal blocks. Lidocaine is associated with cauda equina syndrome and reticulopathy when administered via the spine and is no longer used in that manner. Additionally, lidocaine, even at commercially available concentrations, can be neurotoxic when used for spinal anesthesia. When a patient is placed on an intrathecal pain pump, these solutions often contain several medications; however, bupivacaine would be used as it is longer acting; 1 SME stated, “We wouldn’t use lidocaine.” Lidocaine can be administered with propofol to reduce stinging associated with propofol administration and to suppress airway responses. Postoperatively, lidocaine can be infused in the wound bed and used on intact skin for centralized neuropathic pain. Lidocaine is used frequently in the emergency department (ED) for pediatric patients to numb an area in children fearful of injections.

One SME commented on the use of lidocaine as a topical product to treat vulvodynia but stated that “the problem with the use of lidocaine in a topical product is that you often get reactive pain or pain that gets worse when it wears off. So, you get some relief from say burning and pain. And then you get relief for a couple of hours or a few hours and then you get worse off when you get a second round of pain. So, lidocaine is a somewhat problematic product.”

Local anesthetics are common in dermatology prior to a procedure. The SME had used EMLA® in the past, but no longer uses it currently. Prior to laser procedures a topical anesthetic applied 1-2 hours prior to the procedure can be useful; however, the SME stated that they do not perform a lot of laser procedures. The SME mostly performs Mohs surgeries, and while a topical anesthetic can be used, “if you inject lidocaine, well, there’s not a whole lot of injection pain with it. And so there’s not a lot of benefit to putting a topical on first. Plus the topicals take time, quite a bit of time, actually, to start the numbing. It’s just not efficient to be doing that.”

Several of the SMEs were not familiar with the nominated combinations containing lidocaine. One SME had worked in a dental office where a compounded topical anesthetic was used; it was a gel with lidocaine, tetracaine, and butacaine. The SME also commented that some dentists will have a lidocaine 10%/prilocaine 10%/tetracaine 4%/phenylephrine 2% product compounded stating that “almost every dentist that I’ve met that will have something compounded... want lidocaine and tetracaine together in the mix.” Adding tetracaine allows a faster onset and a longer duration of action. Additionally, dental hygiene can mean blood loss for the patient. The addition of a vasoconstrictor, such as phenylephrine, can make the patient more comfortable, allow the hygienist to perform well, reduce the risk of toxicity, and increase

the duration of action. Another SME commented that lidocaine/epinephrine/tetracaine (LET) is the preferred product for skin grafts, and that while EMLA<sup>®</sup> is commercially available, it is only available in 1 concentration. Compounded products are needed to provide additional options. The SME is interested in a combination product that contains an NSAID and gabapentin or a gabapentinoid to treat peripheral neuropathy. Some practitioners like to combine different “caines” together, with 1 SME commenting that this makes sense “because they have different sorts of onset of action.” Practitioners may have preferred combination products, but 1 SME stated, “I don’t think that there are huge differences in these from what’s commercially available. It’s hard for me to imagine that one of these is so much more important. Like that there’s a use for one of these that can’t be filled by one of the commercially available mixes.” The SME also expressed concern with the concentrations included, stating “One of the issues with these, the caines, is that they can cause methemoglobinemia, and there have been reports of that occurring after topical application. I think that that is a risk, particularly with the sort of higher concentrations. These caines are also metabolized in the same pathway. When you ramp up the concentration of both of them, you’re really probably risking overloading that the metabolism.” Some of the combinations are also used as premedication prior to tattooing. One SME commented on the combination with chamomile, fluocinolone, lidocaine, and witch hazel, stating that they were unsure what it was being used to treat.

As part of Phase 3, 2 nominators provided additional information regarding the products that will be compounded using lidocaine HCl.

Lidocaine 1%/fluocinolone acetonide 0.025% will be compounded as a topical gel to treat symptoms of topical fungal infections applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, benzalkonium chloride, boric acid, methylparaben, propylene glycol, talc, trolamine, white petrolatum, hypromellose, and propylparaben, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants, and their hazardous concerns include allergen; classified as expected to be toxic or harmful; classified as skin irritant; contamination concerns; human endocrine disruptor; human immune and respiratory toxicant or allergen; human irritant; human respiratory irritant; human skin toxicant or allergen; and human toxicant or allergen. In addition, they are restricted in cosmetics (recommendations or requirements) use, concentration, or manufacturing restrictions; as well as violation of industry recommendations – restricted in cosmetics use, concentration, or manufacturing restrictions, and not safe for use on injured or damaged skin. Fluocinolone acetonide is added for its anti-inflammatory properties and niacinamide for its skin-conditioning benefits; reason for adding lidocaine was not provided. This product is needed as it will most likely result in a clinical difference to patients as it does not include the harmful excipients found in FDA-approved drug products, and this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Lidocaine HCl monohydrate 1%/chamomile extract 2%/fluocinolone acetonide 0.025%/witch hazel 5% will not be compounded as the formula has been discontinued.

Lidocaine will be compounded as a 4% ophthalmic solution for use as a preoperative anesthetic. This product is used by practitioners as a non-patient-specific compounded product in operating rooms (ORs). A compounded product is needed because there is no commercially available topical ophthalmic solution at this concentration. The compounded formulation allows for the administration of a topical anesthetic in a concentration desired by the practitioner; in the form of a solution that is formulated for topical ophthalmic use. This includes testing the product to ensure it falls within pH and subvisible particulate requirements for an ophthalmic solution.

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

While a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtained varied from less than 1% to the majority of compounded products used at 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 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 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 already 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 also impacted the operations of hospitals with 1 participant who stated, “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 cleanroom; 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 midsize hospitals being able “to operationalize testing compounds we make for extended stability.” One participant stated, “We might make our own syringes if we could get extended dating, but I believe my operations colleagues don’t always know how to do this and adhere to the letter of the law.”

One participant also commented on the impact that The Joint Commission has had on 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 ORs 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 would be expected that they would have similar needs regarding the concentrations and volumes of products used. However, the products used in a facility are often developed in-house over decades based on physician and nurse

requests, and more recently, appropriateness for an automated dispensing cabinet. As a result, 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 shouldn’t be 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 <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 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 the pharmacy, and they use the del Nido formulation 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*

The survey was not approved for distribution by any professional medical associations.

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 reasons) obtained drug products from outsourcing facilities due to a need for ready-to-use products, and 20 respondents (14%) obtained drug products from outsourcing facilities due to backorders (refer to Table 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 (7.4% of 108 responses, where respondents were allowed to select multiple drug products) obtained lidocaine HCl from a 503B outsourcing facility (refer to Table 19).

Table 11. Characteristics of survey respondents

*Survey not distributed by any professional medical associations*

Table 12. Compounded products prescribed or administered

*Survey not distributed by any professional medical associations*

Table 13. Reasons for using compounded products

*Survey not distributed by any professional medical associations*

Table 14. Stock of non-patient-specific compounded products

*Survey not distributed by any professional medical associations*

Table 15. Obtainment of compounded topical products

*Survey not distributed by any professional medical associations*

Table 16. Demographics of prequestionnaire respondents' facilities

<b>Type of Facility</b>	<b>Responses, n (N = 102)<sup>a</sup></b>
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 <sup>b</sup>	4
Trauma center	5
Urban hospital	5
<b>Number of Beds</b>	<b>Responses, n (N = 39)</b>
< 50	4
50-99	3
100-199	1
200-299	4
300-399	5
400-599	3
> 600	19

<sup>a</sup>Respondents allowed to select more than one type of facility.

<sup>b</sup>Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, and oncology.

Table 17. Reasons for obtaining products from outsourcing facilities

<b>Categories</b>	<b>Responses, n (N = 143)<sup>a</sup></b>
Backorders	20
Convenience	19
Cost	10
Need for concentrations not commercially available	19
Need for multi-ingredient products not commercially available	10
Need for preservative-free products	3
Need for ready-to-use products	27
No FDA-approved product available	7

No on-site compounding facility	1
On-site compounding facility not equipped to compound all necessary products	19
Other <sup>b</sup>	8

<sup>a</sup>Respondents allowed to select multiple categories.

<sup>b</sup>Respondents reported staffing shortages, need for extended dating, volume of product used, standardization projects as additional reasons for using outsourcing facilities.

Table 18. Categories of products obtained from outsourcing facilities

Categories	Responses, n (N=142) <sup>a</sup>
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 <sup>b</sup>	6

<sup>a</sup>Respondents allowed to select multiple categories.

<sup>b</sup>Respondents reported obtaining alum for bladder irrigation, oxytocin, anticoagulant sodium citrate solution, narcotic drips, high-cost antiseizure medications, antiviral medications, topical pain, and oral tablets/capsules.

Table 19. Products obtained from an outsourcing facility

Product	Responses, n (N = 108) <sup>a</sup>
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

<sup>a</sup>Respondents were allowed to select multiple products.

## CONCLUSION

Lidocaine HCl was nominated for inclusion on the 503B Bulks List as a nasal, ophthalmic, topical, dental, rectal, and injectable product in strengths ranging from 0.03-5% for use as an anesthetic, treatment of severe pain, status epilepticus, stomatitis, certain cardiac arrhythmias, and symptoms of topical fungal infections. Lidocaine HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, the UK, and the US.

No literature review was conducted.

From the interviews, lidocaine is used topically in a variety of medical specialties in multiple practice settings as a local anesthetic administered prior to a procedure. In ophthalmology, a topical lidocaine gel is used as a local anesthetic and a compounded preservative-free lidocaine/epinephrine solution is used as an intraocular injection to provide anesthesia and dilation during cataract surgery. In dentistry, 1 SME commented on the use of a combination product that contained lidocaine 10%/prilocaine 10%/tetracaine 4%/phenylephrine 2% stating that dentists like to use lidocaine in combination with tetracaine to provide both a quick onset and long duration of action. Topical lidocaine is also effective for use in children to numb the area prior to receiving an injection. Lidocaine is not administered intrathecally due to the risk of cauda equina syndrome and reticulopathy. For spinal anesthesia and for use in intrathecal pain pumps, bupivacaine is the preferred agent and is the only anesthetic that is FDA-approved for spinal administration. One SME was concerned with the high concentrations for some of the nominated combination products, and was unsure what the chamomile, fluocinolone, lidocaine, and witch hazel combination product was being used to treat.

As part of Phase 3, 2 nominators provided additional information regarding the products that will be compounded using lidocaine HCl. Lidocaine 1%/fluocinolone acetonide 0.025% will be compounded as a topical gel to treat symptoms of topical fungal infections applied multiple times throughout the day for multiple days. Lidocaine HCl monohydrate 1%/chamomile extract 2%/fluocinolone acetonide 0.025%/witch hazel 5% will not be compounded as the formula has been discontinued. Lidocaine will be compounded as a 4% ophthalmic solution for use as a preoperative anesthetic.

The survey was not approved for distribution by any professional medical associations. From the prequestionnaire, 8 respondents obtained lidocaine HCl from a 503B outsourcing facility.

## REFERENCES

1. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. *International Journal of Social Research Methodology: Theory and Practice*. 2005;8(1):19-32.
2. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol*. 2014;67(12):1291-1294.
3. Levac D, Colquhoun H, O'Brien KK. Scoping studies: Advancing the methodology. *Implementation Science*. 2010;5(1).
4. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *International Journal of Evidence-Based Healthcare*. 2015;13(3):141-146.
5. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol*. 2018;18(1):143-143.
6. Antunes AA, Calado AA, Lima MC, Falcão E. Efficacy of intrarectal lidocaine hydrochloride gel for pain control in patients undergoing transrectal prostate biopsy. *Int Braz J Urol*. 2004;30(5):380-383.
7. Beshay SM, Rivera G, Balthasar J, Florea N. Efficacy and clinical value of commonly used ingredients in pain management compounds: A literature review. *Int J Pharm Compd*. 2015;19(4):295-300.
8. Bolt P, Barnett P, Babl FE, Sharwood LN. Topical lignocaine for pain relief in acute otitis media: results of a double-blind placebo-controlled randomised trial. *Arch Dis Child*. 2008;93(1):40-44.
9. Eidelman A, Weiss JM, Baldwin CL, Enu IK, McNicol ED, Carr DB. Topical anaesthetics for repair of dermal laceration. *Cochrane Database Syst Rev*. 2011(6):Cd005364.
10. Gordh T. Lidocaine: the origin of a modern local anesthetic. 1949. *Anesthesiology*. 2010;113(6):1433-1437.
11. Han KR, Kim C, Chae YJ, Kim DW. Efficacy and safety of high concentration lidocaine for trigeminal nerve block in patients with trigeminal neuralgia. *Int J Clin Pract*. 2008;62(2):248-254.
12. Hunt LW, Frigas E, Butterfield JH, et al. Treatment of asthma with nebulized lidocaine: a randomized, placebo-controlled study. *J Allergy Clin Immunol*. 2004;113(5):853-859.
13. Kanai A, Suzuki A, Kobayashi M, Hoka S. Intranasal lidocaine 8% spray for second-division trigeminal neuralgia. *Br J Anaesth*. 2006;97(4):559-563.
14. Lebedevs TH, Wojnar-Horton RE, Yapp P, et al. Excretion of lignocaine and its metabolite monoethylglycinexylidide in breast milk following its use in a dental procedure. A case report. *J Clin Periodontol*. 1993;20(8):606-608.
15. Loyd AV. Lidocaine HCl 2% solution for iontophoresis. *Int J Pharm Compd*. 1997;1(6):416.
16. Loyd AV. Lidocaine HCl 2%, misoprostol 0.003%, and phenytoin 2.5% topical gel for decubitus ulcers. *Int J Pharm Compd*. 2000;4(4):301.
17. Martín-Moro JG, Gallardo JZ. On the mydriatic effect of lidocaine. *J Craniofac Surg*. 2013;24(4):1504.
18. Masket S, Gokmen F. Efficacy and safety of intracameral lidocaine as a supplement to topical anesthesia. *J Cataract Refract Surg*. 1998;24(7):956-960.

19. Mironer YE, Haasis JC, Chapple I, Brown C, Satterthwaite JR. Efficacy and safety of intrathecal opioid/bupivacaine mixture in chronic nonmalignant pain: A double blind, randomized, crossover, multicenter study by the National Forum of Independent Pain Clinicians (NFIPC). *Neuromodulation*. 2002;5(4):208-213.
20. Scavone JM, Greenblatt DJ, Fraser DG. The bioavailability of intranasal lignocaine. *Br J Clin Pharmacol*. 1989;28(6):722-724.
21. Storms ML, Stewart JT, Warren FW. Stability of lidocaine hydrochloride injection at ambient temperature and 4 degrees C in polypropylene syringes. *Int J Pharm Compd*. 2002;6(5):388-390.
22. Tarver CP, Noorily AD, Sakai CS. A comparison of cocaine vs. lidocaine with oxymetazoline for use in nasal procedures. *Otolaryngol Head Neck Surg*. 1993;109(4):653-659.
23. Wolff M, Schnöbel-Eehalt R, Mühlhling J, Weigand MA, Olschewski A. Mechanisms of lidocaine's action on subtypes of spinal dorsal horn neurons subject to the diverse roles of Na(+) and K(+) channels in action potential generation. *Anesth Analg*. 2014;119(2):463-470.
24. Beecham GB, Bansal P, Nessel TA, Goyal A. Lidocaine. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2020.
25. Food and Drug Administration. Drug Shortages. U.S. Food and Drug Administration (FDA). <https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages>. Updated January 29, 2021. Accessed February 15, 2021.
26. University of Utah Drug Information Service. Current Drug Shortages. American Society of Health-System Pharmacists (ASHP). <https://www.ashp.org/Drug-Shortages/Current-Shortages>. Accessed February 15, 2021.
27. Pediatric continuous infusion standards. American Society of Health-System Pharmacists (ASHP). <https://www.ashp.org/-/media/assets/pharmacy-practice/s4s/docs/Pediatric-Infusion-Standards.ashx>. Updated December 2020. Accessed January 13, 2021.
28. Adult continuous infusion standards. American Society of Health-System Pharmacists (ASHP). <https://www.ashp.org/-/media/assets/pharmacy-practice/s4s/docs/Adult-Infusion-Standards.ashx>. Updated November 2016. Accessed January 13, 2021.

## **APPENDICES**

### *Appendix 1. Search strategies for bibliographic databases*

No literature review was conducted.

*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)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Do you prescribe or administer any of the following as a compounded topical product? (please check all that apply)

- Betamethasone acetate
- Betamethasone dipropionate
- Betamethasone sodium phosphate
- Cholestyramine resin
- Cimetidine
- Clobetasol propionate
- Clotrimazole
- Cromolyn sodium
- Dexamethasone sodium phosphate
- Diclofenac sodium
- Finasteride
- Fluconazole
- Fluticasone propionate
- Hydrocortisone
- Itraconazole
- Ketoconazole
- Lidocaine hydrochloride
- Methylprednisolone acetate
- Metronidazole
- Mupirocin
- Niacinamide
- Phytonadione (vitamin K1)
- Prilocaine
- Spironolactone
- Sulfacetamide sodium monohydrate
- Terbinafine hydrochloride
- Tetracaine hydrochloride
- Triamcinolone acetonide
- Zinc oxide

- None of the above
3. Do you prescribe the compounded topical products that you selected in combination with other active pharmaceutical ingredients as a multi-ingredient product?
    - Yes
    - No
    - I'm not sure
  4. Why do you use the compounded topical products that you selected? (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 these products
    - Other (please explain) \_\_\_\_\_
  5. Do you stock non-patient-specific compounded products at your practice?
    - Yes
    - No
    - I'm not sure
  6. I obtain compounded products 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) \_\_\_\_\_
  7. 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) \_\_\_\_\_
  8. What degree do you hold? (please check all that apply)
    - Doctor of Medicine (MD)
    - Doctor of Osteopathic Medicine (DO)
    - Doctor of Medicine in Dentistry (DMD/DDS)
    - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - Naturopathic Doctor (ND)
    - Nurse Practitioner (NP)
    - Physician Assistant (PA)
    - Other (please describe) \_\_\_\_\_

*Appendix 2.2. Survey instrument for pharmacy roundtable prequestionnaire*

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

- Fluids
  - Ophthalmic preparations
  - Patient-controlled analgesia
  - Ready-to-use anesthesia syringes
  - Ready-to-use antibiotic syringes and/or bags
  - Ready-to-use electrolyte solutions
  - Ready-to-use vasopressor solutions
  - Total parenteral nutrition solutions
  - Other, please identify \_\_\_\_\_
7. From the list below, please select the drug(s) that you obtain as either a single-ingredient or multi-ingredient product from an outsourcing facility.
- Acetylcysteine
  - Adenosine
  - Aluminum potassium sulfate
  - Aspartic acid
  - Atenolol
  - Atropine
  - Baclofen
  - Betamethasone
  - Biotin
  - Bupivacaine
  - Calcium chloride
  - Caffeine sodium benzoate
  - Cholecalciferol
  - Chromium chloride
  - Clonidine
  - Dexamethasone sodium phosphate
  - Diclofenac
  - Gentamicin
  - Glycerin
  - Hydroxyzine
  - Ketamine
  - Levocarnitine
  - Lidocaine
  - Lorazepam
  - Magnesium sulfate
  - Manganese chloride
  - Methylprednisolone
  - Midazolam
  - Mupirocin
  - Norepinephrine
  - Ondansetron
  - Phytonadione
  - Potassium chloride
  - Potassium phosphate
  - Prilocaine
  - Proline
  - Propranolol
  - Ropivacaine
  - Sodium chloride
  - Sodium citrate

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

*Appendix 3. Survey distribution to professional associations*

<b>Specialty</b>	<b>Association<sup>a</sup></b>	<b>Agreed/Declined, Reason for Declining</b>
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

<sup>a</sup>Associations that declined in Year 1 and/or Year 2 were not contacted in Year 3.