

# Summary Report

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## Atropine sulfate

### 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

API	Active Pharmaceutical Ingredient
ASHP	American Society of Health-System Pharmacists
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

## INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in its evaluation of the use of atropine sulfate (UNII code: 03J5ZE7KA5), 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 atropine sulfate 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 atropine sulfate has been used historically and currently.<sup>1-3</sup> Assessments 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 atropine sulfate 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

Atropine sulfate was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society (SSPS) and US Compounding Pharmacy.

Atropine sulfate was nominated for use as an intravenous, intramuscular, and subcutaneous injection in concentrations ranging from 0.1 to 1 mg/mL diluted into potential diluents such as sterile water for injection, sodium chloride, dextrose, lactated Ringer's, and dextrose/lactated Ringer's. US Compounding Pharmacy also indicated a need to compound preservative-free solutions.

Atropine sulfate will be used for a variety of indications including:

- Biliary colic
- Cycloplegic refraction
- Gastrointestinal tract spasm
- Mydriasis induction
- Ureteric colic
- Uveitis
- As an antisialagogue when reduction of secretions of the respiratory tract are thought to be needed; its routine use as a preanesthetic agent is discouraged.
- To blunt the increased vagal tone (decreased pulse and blood pressure) produced by intraabdominal traction or ocular muscle traction, its routine use to prevent such events is discouraged.
- To temporarily increase heart rate or decrease atrioventricular (AV) block until definitive intervention can take place, when bradycardias or AV block are judged to be hemodynamically significant and thought to be due to excess vagal tone.
- As an antidote for inadvertent overdose of cholinergic drugs or for cholinesterase poisoning such as from organophosphorus insecticides.
- As an antidote for the "rapid" type of mushroom poisoning due to the presence of the alkaloid muscarine, found in certain species of fungus, such as *Amanita muscaria*.
- To alleviate the muscarinic side effects of anticholinesterase drugs used for reversal of neuromuscular blockade.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of atropine sulfate.<sup>6,7</sup>

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

- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes and/or final product containers for administration.
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical size batch for outsourcing facilities; a single vessel compounded from bulk Active Pharmaceutical Ingredient (API) is safer and more efficient than unmanageable amounts of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100 percent potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- In order to utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.
- Manufacturer backorder.

## **METHODOLOGY**

### *Background information*

The national medicine registers of 13 countries and regions were searched to establish the availability of atropine sulfate products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in the 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 atropine sulfate; name variations of atropine sulfate were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing atropine sulfate. 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*

Atropine sulfate 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 atropine sulfate was used in a clinical setting. Indications from the nominations were reviewed to identify medical specialties that would potentially use atropine sulfate. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided verbal informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

In addition to interviews with individual SMEs, a roundtable discussion with pharmacists was held. Participants were identified through outreach to professional associations that would potentially purchase compounded products from outsourcing facilities. A prequestionnaire was distributed to those who agreed to participate to collect information about the types of facilities at which participants worked and the products they purchased from outsourcing facilities (refer to Appendix 2 for complete survey and *Results of survey* section for results of prequestionnaire). The roundtable lasted 60 minutes and was conducted via Zoom, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

### *Survey*

A survey was distributed to the members of professional medical associations to determine the use of atropine sulfate 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*

- Atropine sulfate is available as an FDA-approved product in the nominated dosage form and ROA.
- Atropine sulfate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for atropine sulfate.
- Atropine sulfate 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>
Atropine sulfate	0.05-2.86 mg/mL	Solution	Endotracheal Intramuscular Intraosseous Intravenous Subcutaneous	Prescription	Approved prior to 1/1/1982

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

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



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

Active Ingredient <sup>b</sup>	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date <sup>c</sup>
Atropine sulfate	0.05-1.2 mg/mL	Solution	Intramuscular Intravenous Subcutaneous	Abu Dhabi	Active	–
				Australia	Prescription-only medication	8/13/1991
				Belgium	Prescription	7/9/2009
				Canada	Prescription	12/31/1975
				Hong Kong	Prescription-only medicine	11/29/2000
				Ireland	Prescription-only nonrenewable	7/24/2015
				Latvia	Prescription	10/28/2005
				Namibia	–	12/26/1976
				New Zealand	Prescription	8/10/2017
				Saudi Arabia	Prescription	–
				United Kingdom	Prescription-only medication	4/19/1989

Abbreviations: –, not provided; US, United States.

<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>Atropine sulfate used as the standard for name variations, including atropine and atropine sulfas.

<sup>c</sup>If multiple approval dates and/or multiple strengths, then earliest date provided.

### *Results of literature review*

No literature review was conducted.

### Characteristics of included studies

No literature review was conducted.

### Use of atropine sulfate

No literature review was conducted.

### Pharmacology and historical use

Additional references were found that provided information about the current availability of atropine sulfate.

Both the FDA Drug Shortages list and the American Society of Health-System Pharmacists (ASHP) Current Drug shortages list included atropine sulfate injection products.<sup>8,9</sup> The FDA list included 0.4 to 1-mg/mL vials, 0.1 mg/10 mL–prefilled syringes, and 0.05 to 0.1-mg/mL plastic and glass syringes (date first posted not available).<sup>8</sup> The ASHP list included a 0.1-mg/mL injection in a 10-mL Ansyr syringe (first posted August 2, 2011).<sup>9</sup> ASHP mentions that this is a Pfizer product available in limited supply.<sup>9</sup> The reasons provided for these shortages included increased demand for the product, manufacturing delays, and “other.”<sup>8,9</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

*No combination products were nominated.*

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. One SME discussed atropine sulfate. The SME was a medical doctor, specializing and/or board-certified in anesthesiology working in a community hospital. The SME had been in practice for 25 years.

Atropine is commonly used for bradycardia if either glycopyrrolate does not work or if the heart rate is extremely low. For mild decreases in heart rate glycopyrrolate or epinephrine are typically used first. Since bradycardia is considered an emergency, administration of atropine should be given as quickly as possible—so there is a need for a ready-to-use product. However, atropine is currently available as a 0.1 mg/mL unit of use syringe. Historically, atropine has been used as a reversing agent for nondepolarizing muscle relaxants, but this is not done frequently anymore. Currently, suggamadex is the agent typically used.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. Forty-three participants attended the event; refer to Table 15 for characteristics of the facilities that the participants represented. A prequestionnaire was also distributed to participants; refer to Tables 15-18 for results of the prequestionnaire.

While a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtained varied from less than 1% to the majority of compounded products used at one participant's facility. A participant stated, "We have this method that we use where if we can buy it commercially ready to administer, we do that. If we can't buy it in that format, then we buy it in a vial, for example, that can be snapped into a Mini-Bag Plus because we're a Baxter house, as a second preference. If we can't buy it in either of those two formats and we can get it from a 503B, then we do that. And our last resort is compounding internally." Two participants commented that they will not outsource a product unless 2 outsourcing facilities that they contract with are able to compound the product. This redundancy will allow for a quick flip to the other outsourcing facility if there is an issue with a product compounded from 1 outsourcing facility, minimizing the impact to the participant's facility.

Participants were asked to discuss the decision-making process used at their facility to determine what products to obtain from an outsourcing facility. One major theme that emerged from this discussion was that many of the products purchased from outsourcing facilities are used in critical care areas, like emergency departments and operating rooms. Participants commented that outsourcing facilities are able to provide ready-to-use products that have longer beyond-use dates compared to products compounded in-house, allowing these products to be stocked in automated dispensing cabinets in these units. One participant commented that "we're always going to outsource a PCA [patient-controlled analgesia] syringe because we can store it in a Pyxis machine versus us making it and storing it in a fridge." Another participant commented on the benefits of storing medications in an automated dispensing cabinet, stating that "operationally, if you have a stat medication or something that needs to be delivered within 10 to 15 minutes, if you're looking at us doing it, you're looking at a 5-minute gown and glove. If we don't have somebody in the IV [intravenous] room, if you're doing 797 right, it's 5 minutes. It's 4 minutes to tube it. It's 3 minutes to make it, and then you have a dosage system or a camera system, a few minutes more. We are not able to meet that need or they're just contaminating the IV room if they are trying to do it."

Having ready-to-use products available also minimizes the need for compounding and product manipulations to occur on the floor. This can be especially beneficial in children's hospitals as they face a unique need in that they are already having to perform a lot of manipulations to products due to a lack of

concentrations or sizes available. One participant commented that “at baseline, already, we manipulate about 80% of what we dispense to patients” and another stated that “there’s a number of drugs that require additional manipulation, to get them to a concentration that’s appropriate for kids.” One participant stated that “we’re trying to minimize compounding, expedite actual therapies to patients in that setting [operating room], minimize manipulations as much as possible.” Similarly in the emergency department, one participant stated they prefer ready-to-use products for some floor-stock items, like vasopressor infusions, to prevent compounding from occurring on the floor, and another commented that “we absolutely buy as many pressor drips as we can.” One participant remarked that they have received requests from anesthesiologists for products that are commercially available in vials that require manipulation prior to administration to be purchased as syringes from outsourcing facilities stating that “they would prefer to have a syringe form.”

Another theme regarding deciding what products to purchase from an outsourcing facility was focused on the utilization and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, like the emergency department and operating room, typically have a high product utilization and overall turnover, leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency 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 stated that, while they do not obtain a lot of products from outsourcing facilities, “when we do purchase from 503Bs, typically it would be if we just don’t have the capacity to keep up with what the demand is.” One participant also commented that they will obtain labor-intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The coronavirus disease 2019 (COVID-19) pandemic has also impacted the operations of hospitals, as noted by 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 cleanroom and therefore perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use date that can be assigned to these products and, as the participant stated, “We obviously need to provide product with much extensive beyond use dating than we can provide.” Several participants also commented that they do not perform high-risk compounding in-house, and therefore, all of these products are outsourced. There are challenges with midsize hospitals being able “to operationalize testing compounds we make for extended stability.” One participant stated, “We might make our own syringes if we could get extended dating, but I believe my operations’ colleagues don’t always know how to do this and adhere to the letter of the law.”

One participant also commented on the impact that The Joint Commission has had on pushing pharmacies to obtain products from outsourcing facilities. The 2018 medication management standard MM.05.01.07 was intended to move IV admixture preparation out of the nursing unit. This forced pharmacies to consider strategies to make IV admixtures available for use on the floor. Additionally, NPSG.03.04.01 states that all medications and solutions should be adequately labeled, including in the operating room and other settings in which procedures are performed. USP <795> and <797> are applicable in operating room settings, stating that products should be labeled and used within 1 hour, which may be problematic if syringes are drawn up at the beginning of the day and cases are canceled or delayed. The participant also commented on the cost related to purchasing premade products from manufacturers, stating that “predatory pricing on premixes is present in the market.”

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products utilized. However, the products utilized in a facility are often developed in-house over decades based on physician and nurse requests, and, more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, “These practices had evolved somewhat disparately; even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines.” This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, “I think we made 9 different epidural concentrations, all driven by anesthesia, and they want what they want and 503Bs may not offer that. No one else in the country is buying that same concentration; a 503B isn’t going to go through the expense of adding that to their product list.” The participant continued that “similar with the ADCs [automated dispensing cabinets], we’ve run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, ‘No, we can’t have it, and that’s too big it won’t fit,’ we want it in this format—and then we’re stuck again because there’s no 503B offering a format during that shortage that fits where it needs to go. Then we’re stuck in sourcing.” Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that “3% saline for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We’re either going to draw that out or we’re sending it to the ER with stickers all over it saying only give 150 [mL].” The participant continued that “it would be great if the FDA could look at the size of the container that they’re approving and whether that’s a realistic dose; is it a unit dose or isn’t it?”

Participants had differing opinions on the use of outsourcing facilities to obtain drugs during a shortage. Several participants stated that they will typically first restrict use of a drug on shortage, in order to conserve supply, before turning to an outsourcing facility. One participant commented that “most of the time, I will probably pursue restricting, conserving, and looking at all available options prior to going to an outsourcer on my end,” and another stated, “I can only think of one time in recent history where we went to an outsourcer.” One participant commented that “503Bs can’t accept the additional volume if it’s a true shortage. If you’re not with them preshortage, you’re not going to get products when you need it during the shortage,” continuing that “typically in a shortage, you learn to live without them. You have to.” Additionally, in the event of the shortage being the result of lack of an API, outsourcing facilities are likely to be equally affected and unable to provide assistance. However, one participant stated that they first began working with outsourcing facilities because of shortages. This participant commented that “what the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on API. If sterile becomes short, they quickly switch to producing through API, which ASHP

[American Society of Health-System Pharmacists] and the FDA allows.” This “adds a lot of flexibility so they can bounce back and forth and really try to insulate us from shortages.”

A few participants commented on the use of API by outsourcing facilities. One commented that as long as they are conducting end-product sterility and stability testing and the product meets quality standards, they are not concerned with the starting ingredients. As long as buyers are familiar with regulations and know what to look for, another participant commented, there should not be any issues with purchasing products compounded starting from API. Another participant stated that as more outsourcing facilities began using API, they became more comfortable with them doing so. However, one participant observed that most outsourcing facilities are switching to sterile-to-sterile and only using API if there is a shortage, stating, “I think the FDA has really looked closely at API, and they’re slowly pushing the 503B outsourcers to a sterile-to-sterile.” Only 1 participant commented that they prefer sterile-to-sterile. Another participant stated that the companies they use are all sterile-to-sterile.

A few participants commented on the need for preservative-free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative-containing product. So, there is a need for this product to be compounded from API as a preservative-free product. One participant stated that “if there’s not a preservative-free containing option, it really should be something that should be able to be compounded from 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 are not able to, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products, but when they reviewed the facilities, they did not pass their internal quality standards; 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 cleanroom with a dedicated HVAC [heating, ventilation, and air conditioning], so you’re talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn’t there.” Another participant stated that the concentrations required for ophthalmic antibiotics are not available, but the labor and risk of compounding these products in-house is not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. LET (lidocaine-epinephrine-tetracaine) gel, for use as a topical anesthetic, was the most commonly obtained product along with buffered lidocaine to put in J-Tips. Another participant stated that they obtain diclofenac suppositories from an outsourcing facility due to the high cost of indomethacin suppositories. One participant commented that most of the products they outsource are nonsterile products, generally for oral or topical administration due to a lack of commercially available products being available. The participant stated that they purchase low-dose naltrexone for oral use in patients with refractory fibromyalgia and ketamine troches for patients with chronic pain. The participant continued that, while the evidence does not support many of the ingredients used in topical pain products, “However, there are select patients. It’s very rare that taking that cream away from them actually causes more harm than good.” A few participants commented that there is a gap in the market for nonsterile products with 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 nonsterile ingredients; however, there had been challenges with crystallization after storage. A few participants commented that there is a sterile alum powder available, which they purchase to compound in-house. One participant had concerns regarding this powder, stating that “I’ve talked to that company, but I’ve had some concerns for them because they don’t sell it as a drug. The owner was selling you a chemical; we’re selling you a bulk API. It’s just sterile. They were fuzzy and I never followed up, but when I asked about their process for verifying the sterility, as you would with a sterile product—we do USP <71> Sterility Testing—they couldn’t really give me an answer. They just say they tested for sterility.” The participants commented that alum is only needed a few times a year. However, as one participant observed, “When you need it, it’s an emergency,” and another noted that it “is a challenge for anybody who has the cyclophosphamide-induced hemorrhagic cystitis.” As a result, one participant maintains a small inventory of alum product that is purchased from an outsourcing facility, but “more times than not, they go unused and expire.” Another stated that they do not keep it in stock because there is a minimum purchase and there are only a few cases a year for whom they need to use alum. The participant had it stat shipped when needed. Another participant stated that “we had a meeting with the head of urology who was baffled why they’re even ordering it. He was like, ‘This is an old, really old. I don’t even know why we’re using it’ and basically approved for us to not even make it anymore for now.”

Two participants commented on the use of glycerin at their facility. One stated that they purchase it from a 503A because they were not able to find an outsourcing facility that provides this product. The participant commented that glycerin is used in 3 different concentrations at their facility, 1 for ophthalmic use, 1 for neurologic use in trigeminal neuralgia, and 1 for instilling into “a very specific kind of pump that’s used to deliver a very specific kind of chemotherapy.” When there are breaks in the chemotherapy regimen, the pump has to be filled with something, and by using glycerin “it can go 3 months or something like that, so it’s a huge patient satisfier to have that concentration available.” The participant also commented that since they have been unable to find an outsourcing facility that compounds the concentration needed for trigeminal neuralgia, they have patients who have been waiting years for treatment. The other participant stated that they compound it in-house but said that it is not done very frequently. The participant commented that it is very difficult to sterilize due to the thickness of the product.

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution in patients undergoing dialysis, with 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 [sic] for pH and potassium testing. Obviously, then we’re confined to 797 beyond-use dates versus longer beyond-use dates that we get from the 503B.” Another participant commented that cardioplegic solutions are managed by the perfusion department, not pharmacy, and they use del Nido solution as well as 3 other formulations.

The participants also discussed challenges with utilizing outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because “it just hasn’t been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to ... It just isn’t worth the dating that they gave us or can give us.” Another commented that they obtain very little product from outsourcing facilities due to “the amount of work for vetting and continually validating quality of these 503B outsourcing facilities.” The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that “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 low and behold they’re shut down, or closed, or whatever it may be.” Minimum purchase amounts were also reported as a concern, with one participant stating that “what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That’s a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients.” Another challenge was related to outsourcing facilities utilizing API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration (DEA) places on the quantity that can be produced. The participant stated that “they [outsourcing facilities] want to buy the product that we’re trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don’t end up with a shortage year after year, after year and then chasing our tail. Also, we may actually want to tell 503Bs, they can’t buy those products or that they’re limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products, because it actually induces the shortage in many ways.”

### *Results of survey*

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

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 2.2 for survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 15 for respondent characteristics. Amongst respondents, 35 (81% of 43 total respondents) utilized outsourcing facilities to obtain drug products, 4 (9%) did not utilize outsourcing facilities, and 4 (9%) did not respond to this question.

Twenty-seven respondents (19% of 143 responses, where respondents were allowed to select multiple reasons) obtained drug products from outsourcing facilities due to a need for ready-to-use products and 20 respondents (14%) obtained drug products from outsourcing facilities due to backorders (refer to Table 16).

Fourteen respondents (31% of 45 total responses, where respondents were allowed to select multiple types) obtained nonsterile products from outsourcing facilities and 31 (69%) obtained sterile products from outsourcing facilities. Refer to Table 17 for the categories of products obtained from outsourcing facilities.

Nine respondents (8% of 108 responses, where respondents were allowed to select multiple drug products) obtained atropine from a 503B outsourcing facility (refer to Table 18).

Table 11. Characteristics of survey respondents

*No respondents to survey distributed via professional medical associations*

Table 12. Conditions for which atropine sulfate prescribed or administered

*No respondents to survey distributed via professional medical associations*

Table 13. Reasons for using compounded atropine sulfate

*No respondents to survey distributed via professional medical associations*

Table 14. Use of non-patient-specific compounded atropine sulfate

*No respondents to survey distributed via professional medical associations*

Table 15. Demographics of prequestionnaire respondents' facilities

Type of Facility	Responses, n (N = 102) <sup>a</sup>
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	5
300-399	5
400-599	3
> 600	19

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

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

Table 16. 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 onsite compounding facility	1
Onsite compounding facility not equipped to compound all necessary products	19
Other <sup>b</sup>	8

<sup>a</sup>Respondents were 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 utilizing outsourcing facilities.

Table 17. Categories of products obtained from outsourcing facilities

<b>Categories</b>	<b>Responses, n (N = 142)<sup>a</sup></b>
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 were 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 18. Products obtained from an outsourcing facility

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

Atropine sulfate was nominated for inclusion on the 503B Bulks List as a solution for intravenous, intramuscular, and subcutaneous injection to treat a variety of conditions. Atropine sulfate 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, atropine sulfate is commonly used to treat bradycardia that is either refractory to glycopyrrolate or epinephrine or extremely low. Bradycardia is considered an emergency, so there is a need for a ready-to-use product, but there is one that is commercially available. Atropine sulfate has been used historically to reverse nondepolarizing muscle relaxants; however, this is not done frequently anymore and instead suggamadex is used for this indication.

Zero people responded to the survey distributed via professional medical associations and available on the project website. From the prequestionnaire, 9 respondents obtained atropine from a 503B outsourcing facility.

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## **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 atropine sulfate to your patients?

- Yes
- No

3. Do you prescribe or administer atropine sulfate by any of the following dosage forms and/or routes of administration? (check all that apply)

- Intravenous, intramuscular, or subcutaneous injection solutions
- None of the above

4. I prescribe or administer atropine sulfate for the following conditions or diseases: (check all that apply)

- Atrioventricular heart block
- Biliary colic
- Bradyarrhythmia
- Cardiac dysrhythmia
- Cycloplegic refraction
- Gastrointestinal tract spasm
- Mydriasis induction
- Organophosphate poisoning
- Premedication for anesthetic procedure
- Mushroom poisoning
- Ureteric colic
- Uveitis
- Other (please explain) \_\_\_\_\_

5. I prescribe or administer compounded atropine sulfate in combination with other active pharmaceutical ingredients as a multi-ingredient product.

- Yes
- No

6. I prescribe or administer atropine sulfate with my patients as the following: (check all that apply)

- FDA-approved drug product
- Compounded drug product
- Other (please explain) \_\_\_\_\_

7. I use compounded atropine sulfate because: (check all that apply)

- Commercial products are not available in the dosage form, strength, or combination I need (please explain) \_\_\_\_\_
  - Patient allergies prevent me from using commercially available products (please explain) \_\_\_\_\_
  - Patient conditions prevent me from using commercially available products (please explain) \_\_\_\_\_
  - I am not aware of any commercially available products containing atropine sulfate
  - Other (please explain) \_\_\_\_\_
8. Do you stock non-patient-specific compounded atropine sulfate at your practice?
- Yes
  - No
  - I'm not sure
9. I obtain compounded atropine sulfate from the following: (check all that apply)
- Compound myself at my practice
  - Have the product compounded by an in-house pharmacy
  - Purchase, or have a patient purchase, from a compounding pharmacy
  - Purchase, or have a patient purchase, from an outsourcing facility
  - Other (please explain) \_\_\_\_\_
10. What is your practice setting? (check all that apply)
- Physician office/private practice
  - Outpatient clinic
  - Hospital/health system
  - Academic medical center
  - Emergency room
  - Operating room
  - Other (please describe) \_\_\_\_\_
11. What degree do you hold? (check all that apply)
- Doctor of Medicine (MD)
  - Doctor of Osteopathic Medicine (DO)
  - Doctor of Medicine in Dentistry (DMD/DDS)
  - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
  - Naturopathic Doctor (ND)
  - Nurse Practitioner (NP)
  - Physician Assistant (PA)
  - Other (please describe) \_\_\_\_\_

*Appendix 2.2. Survey instrument for pharmacy roundtable prequestionnaire*

1. Please select all that apply regarding the facility with which you are affiliated.
  - Academic medical center
  - Acute care hospital
  - Children's hospital
  - Community hospital
  - Critical access hospital
  - Dialysis center
  - Federal government hospital
  - Health system
  - Inpatient rehabilitation center
  - Long-term acute care hospital
  - Outpatient surgery center
  - Rural hospital
  - Skilled nursing facility
  - Specialty hospital, please identify 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*

<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.