Summary Report

Lorazepam

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

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

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Frequently Used Abbreviations

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

INTRODUCTION

This report was created to assist the US Food and Drug Administration (FDA) in its evaluation of the use of lorazepam (UNII code: O26FZP769L), 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 lorazepam is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted, and health care practitioners were consulted to identify how lorazepam has been used historically and currently.[1-3]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.[1,4,5] Rather, the aim was to summarize the available evidence on the use of lorazepam 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

Lorazepam was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA) and the Specialty Sterile Pharmaceutical Society (SSPS).

Lorazepam was nominated as an oral and injectable solution (1-25 mg/mL) to be administered via oral, injectable, intramuscular, and intravenous routes for:

- Agitation
- Alcohol withdrawal
- Amnesia induction
- Anxiety, preprocedural anxiety
- Chemotherapy-induced nausea/vomiting prophylaxis
- Insomnia
- Procedural sedation
- Sedation induction and maintenance
- Seizure prophylaxis
- Status epilepticus

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of lorazepam.[6,7]

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

- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patient need for dosage form or strength, including greater concentration, that is not available commercially.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Manufacturer drug shortages.
- 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.
- 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.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of lorazepam 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 included 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 lorazepam; name variations of lorazepam 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 ROAs 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 lorazepam. 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

Lorazepam 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 lorazepam 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 lorazepam. 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 lorazepam in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Years 1 and 2 were not contacted for project Year 3 surveys.

The survey was posted on the project website, and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes, with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Lorazepam is available as an FDA-approved product in the nominated dosage form and ROA. Lorazepam is also available as an FDA-approved oral tablet.
- Lorazepam is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for lorazepam.
- Lorazepam is available in the nominated dosage form and ROA in Abu Dhabi, Belgium, Canada, Ireland, Latvia, and the UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Lorazepam	2-4 mg/mL	Injectable	Injection	Prescription	Approved prior to 1/01/1982
	2 mg/mL	Concentrate	Oral	Prescription	6/28/1991

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

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Lorazepam	2-4 mg/mL	Liquid, solution	Injection, intramuscular, intravenous	Abu Dhabi	Active	—
				Belgium	Medical prescription	1/25/1977
				Canada	CDSA IV	6/06/2001
				Ireland	Prescription-only (non-renewable)	6/27/1977
				Latvia	Prescription	6/25/2019
				Namibia	—	12/26/1982
				UK	Prescription-only medication	3/12/2009
	1-2 mg/mL	Solution, syrup	Oral	Abu Dhabi	Active	—
				UK	Prescription-only medication	11/29/2016

Abbreviations: —, not provided; CDSA, Controlled Drugs and Substances Act.

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in the English language; and the desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

[b]If multiple approval dates and/or multiple strengths, then the earliest date was provided.

Results of literature review

No literature review was conducted.

Pharmacology and historical use

One reference was found that provided information about the pharmacological or historical use of lorazepam. Additional references were found that provided information about the current availability of lorazepam.

Lorazepam is a benzodiazepine that first went on the market in the US in 1977.[8] It is commonly used in the inpatient setting due to its rapid intravenous onset of action (1-3 minutes) and relatively clean side effect profile.[8] Lorazepam is approved by the FDA for "short-term (4 months) relief of anxiety symptoms related to anxiety disorders, anxiety-associated insomnia, anesthesia premedication in adults to relieve anxiety, or to produce sedation/amnesia, and treatment of status epilepticus."[8] Off-label uses of lorazepam include "rapid tranquilization of the agitated patient, alcohol withdrawal delirium, alcohol withdrawal syndrome, insomnia, panic disorder, delirium, chemotherapy-associated anticipatory nausea and vomiting (adjunct or breakthrough), as well as psychogenic catatonia."[8] Available routes of administration for lorazepam include oral, intravenous, and intramuscular.[8]

Both the FDA Drug Shortages list and the American Society of Health-System Pharmacists (ASHP) Current Drug Shortages list include lorazepam injection (first posted on the FDA site May 3, 2018; ASHP June 23, 2015).[9,10] The reasons provided for this shortage included: discontinuation of manufacturing, increased demand for the product, manufacturing delays, and "other."[9,10] The ASHP website also mentioned a current shortage of lorazepam tablets (October 4, 2018) and a resolved shortage of lorazepam oral solution (from January 31, 2018 to September 26, 2018).[10]

ASHP has the Standardize 4 Safety initiative to develop national standardized concentrations for intravenous medications in both pediatrics and adults.[11,12] For lorazepam, the concentration standard for continuous infusions in adult patients is 1 mg/mL, which is not commercially available.[12] There is no concentration standard for pediatric patients.[11] ASHP states that there is the possibility of concentration and unit mismatch depending on the pharmacy or outsourcing facility label.[11,12]

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 lorazepam. The SME was a medical doctor. The SME specialized and/or was board-certified in anesthesiology, working in a community hospital. The SME had been in practice for 25 years.

In anesthesia, lorazepam is not used frequently because it is longer acting. A shorter-acting medication is preferred, so its action will wear off by the end of the case. Lorazepam is useful taken orally for patients who are anxious or administered as a continuous infusion for patients that are in the intensive care unit (ICU) on a ventilator.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. The event was attended by 43 participants; 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 most 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 would not outsource a product unless 2 outsourcing facilities that they contract with are able to compound the product. This redundancy will allow for a quick flip to the other outsourcing facility if there is an issue with a product compounded from one outsourcing facility, minimizing the impact to the participant's facility.

Participants were asked to discuss the decision-making process used at their facility to determine what products to obtain from an outsourcing facility. One major theme that emerged from this discussion was that many of the products purchased from outsourcing facilities are used in critical care areas, like emergency departments and operating rooms. Participants commented that outsourcing facilities are able to provide ready-to-use products that have longer beyond-use dates compared to products compounded in-house, allowing these products to be stocked in automated dispensing cabinets in these units. One participant commented, "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 already have to perform a lot of manipulations to products due to a lack of concentrations or sizes available. One participant commented, "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, "We're trying to minimize compounding, expedite actual therapies to patients in that setting [operating

room], [and] minimize manipulations as much as possible." Similarly, in the emergency department, 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, and another commented, "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 for deciding what products to purchase from an outsourcing facility 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, like the emergency department and operating room, typically have a high product utilization and overall turnover, leading to several participants turning to outsourcing facilities to obtain products intended for use in these areas. Participants stated that they evaluate the volume of product needed and the frequency with which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant explained, "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 would 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 evaluating pharmacy staff workload, the type of facility and its capabilities also impacted the decision-making process. One participant commented that they do not have an established cleanroom and therefore must perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use date that can be assigned to these products, and as the participant stated, "We obviously need to provide product with much [more] extensive beyond-use dating than we can provide." Several participants also commented that they do not perform high-risk compounding in-house, and therefore, all of these products are outsourced. There are challenges with midsize hospitals being able "to operationalize testing compounds we make for extended stability." One participant stated, "We might make our own syringes if we could get extended dating, but I believe my operations colleagues don't always know how to do this and adhere to the letter of the law."

One participant also commented on the impact 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 them from an outsourcing facility. However, such standardization may not always be possible. One participant stated that you would expect similar facilities to have similar needs regarding the concentrations and volumes of products used. However, the products used in a facility are often developed in-house over decades based on physician and nurse requests and, more recently, appropriateness for an automated dispensing cabinet. As a result, 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 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, "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 insourcing." 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 mentioned 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 the use of a drug on shortage to conserve supply before turning to an outsourcing facility. One participant commented, "Most of the time, I will probably pursue restricting, conserving, and looking at all available options prior to going to an outsourcer on my end," and another stated, "I can only think of one time in recent history where we went to an outsourcer." One participant commented that "503Bs can't accept the additional volume if it's a true shortage. If you're not with them pre-shortage, you're not going to get products when you need it during the shortage," continuing that "typically in a shortage, you learn to live without them. You have to." Additionally, if a shortage is due to a scarce API, outsourcing facilities are likely to be equally affected 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 APIs. If sterile becomes short, they quickly switch to producing through APIs, which the 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 APIs 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. Another explained that as long as buyers are familiar

with the regulations and know what to look for, there should be no issues with purchasing products compounded starting from APIs. Another participant stated that as more outsourcing facilities began using APIs, 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 APIs if there is a shortage, stating, "I think the FDA has really looked closely at APIs, 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 all the companies they use are 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 APIs 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 they have never needed to order preservative-free products 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 are not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. LET (lidocaine-epinephrine-tetracaine) gel, for use as a topical anesthetic, was the most commonly obtained product along with buffered lidocaine to put in J-Tips. Another participant stated that they obtain diclofenac suppositories from an outsourcing facility due to the high cost of indomethacin suppositories. One participant commented that most of the products they outsource are nonsterile products, generally for oral or topical administration, due to a lack of commercially available products 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 added 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 they "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 a sterile alum powder is available, which they purchase to compound in-house. One participant had concerns regarding this powder, stating, "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, 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, "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 reported that they compound it in-house but said that it is not done very frequently, and 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, "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 do not offer the volume needed at their institution. Another participant commented that while they do obtain the del Nido formulation from an outsourcing facility, they also compound a proprietary formulation in-house. This participant observed that "it is complicated to do in-house. We do it on a Baxa 1200 or 2400, either one, compounder. Then we send it up to [sic] for pH and potassium testing. Obviously, then we're confined to 797 beyond-use dates versus longer beyond-use dates that we get from the 503B." Another participant commented that cardioplegic solutions are managed by the perfusion department, not the pharmacy, and they use del Nido solution as well as 3 other formulations.

The participants also discussed challenges when 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 [the] 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 FDA 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, "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 APIs to compound narcotics. One participant commented that this often worsens drug shortages due to the Drug Enforcement Administration (DEA) quotas placed on the quantity that can be produced. The participant stated that the 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

A separate survey was not constructed for lorazepam, and therefore, no survey was distributed via professional medical associations or available on the project website.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 2 for survey instrument).

A total of 43 people responded to the prequestionnaire; refer to Table 15 for respondent characteristics. Among the 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.

There were 27 respondents (19% of 143 responses, where respondents were allowed to select multiple reasons) who obtained drug products from outsourcing facilities due to a need for ready-to-use products, and 20 respondents (14%) obtained drug products from outsourcing facilities due to drug shortages (refer to Table 16).

There were 14 respondents (31% of 45 total responses, where respondents were allowed to select multiple types) who 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.

Two respondents (2% of 108 responses, where respondents were allowed to select multiple drug products) obtained lorazepam from a 503B outsourcing facility (refer to Table 18).

Table 11. Characteristics of survey respondents

No separate survey constructed

Table 12. Conditions for which lorazepam prescribed or administered

No separate survey constructed

Table 13. Reasons for using compounded lorazepam

No separate survey constructed

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

No separate survey constructed

Table 15. Demographics of prequestionnaire respondents' facilities

Type of Facility	**Responses, n (N = 102)**[a]
Academic medical center	15
Acute care hospital	16
Children's hospital	8
Community hospital	11
Critical access hospital	2
Dialysis center	2
Federal government hospital	4
Health system	15

Inpatient rehabilitation center	4
Long-term acute care hospital	3
Outpatient surgery center	6
Rural hospital	2
Skilled nursing facility	0
Specialty hospital[b]	4
Trauma center	5
Urban hospital	5
Number of Beds	**Responses, n (N = 39)**
< 50	4
50-99	3
100-199	1
200-299	4
300-399	5
400-599	3
> 600	19

[a]Respondents were allowed to select more than 1 type of facility.
[b]Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, and oncology.

Table 16. Reasons for obtaining products from outsourcing facilities

Categories	Responses, n (N = 143)[a]
Backorders	20
Convenience	19
Cost	10
Need for concentrations not commercially available	19
Need for multi-ingredient products not commercially available	10
Need for preservative-free products	3

Need for ready-to-use products	27
No FDA-approved product available	7
No onsite compounding facility	1
Onsite compounding facility not equipped to compound all necessary products	19
Other[b]	8

[a]Respondents were allowed to select multiple categories.
[b]Respondents reported staffing shortages, need for extended dating, volume of product used, and standardization projects as additional reasons for utilizing outsourcing facilities.

Table 17. Categories of products obtained from outsourcing facilities

Categories	**Responses, n (N = 142)**[a]
Cardioplegic solutions	14
Dermatologic preparations	6
Dialysate solutions	0
Fluids	8
Ophthalmic preparations	10
Patient-controlled analgesia	20
Ready-to-use anesthesia syringes	25
Ready-to-use antibiotic syringes and/or bags	14
Ready-to-use electrolyte solutions	5
Ready-to-use vasopressor solutions	18
Total parenteral nutrition solutions	16
Other[b]	6

[a]Respondents were allowed to select multiple categories.
[b]Respondents reported obtaining alum for bladder irrigation, oxytocin, anticoagulant sodium citrate solution, narcotic drips, high-cost anti-seizure medications, antiviral medications, topical pain, and oral tablets/capsules.

Table 18. Products obtained from an outsourcing facility

Product	**Responses, n (N = 108)**[a]

Acetylcysteine	1
Adenosine	2
Aluminum potassium sulfate	2
Aspartic acid	0
Atenolol	0
Atropine	9
Baclofen	4
Betamethasone	0
Biotin	0
Bupivacaine	8
Calcium chloride	1
Caffeine sodium benzoate	0
Cholecalciferol	1
Chromium chloride	0
Clonidine	0
Dexamethasone sodium phosphate	0
Diclofenac	0
Gentamicin	0
Glycerin	1
Hydroxyzine	0
Ketamine	14
Levocarnitine	0
Lidocaine	8
Lorazepam	2
Magnesium sulfate	4
Manganese chloride	0

Methylprednisolone	0
Midazolam	15
Mupirocin	1
Norepinephrine	15
Ondansetron	0
Phytonadione	0
Potassium chloride	0
Potassium phosphate	0
Prilocaine	0
Proline	0
Propranolol	1
Ropivacaine	6
Sodium chloride	0
Sodium citrate	3
Sodium phosphate	0
Tetracaine	2
Triamcinolone acetonide	0
Tropicamide	0
None of the above	8

[a]Respondents were allowed to select multiple products.

CONCLUSION

Lorazepam was nominated for inclusion on the 503B Bulks List in the form of oral and injectable products to treat various indications. Lorazepam is available in the nominated dosage forms and ROAs in Abu Dhabi, Belgium, Canada, Ireland, Latvia, the UK, and the US.

No literature review was conducted.

From the interviews, as lorazepam has a longer duration of action, it is therefore not used frequently in anesthesia.

No survey for lorazepam was distributed via professional medical associations. From the prequestionnaire, 2 respondents reported obtaining lorazepam from an outsourcing facility.

REFERENCES

1. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Method.* 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. *Implement Sci.* 2010;5:69.
4. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *Int J Evid Based Healthc.* 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.
6. Foster S, Kessel J, Berman ME, Simpson GM. Efficacy of lorazepam and haloperidol for rapid tranquilization in a psychiatric emergency room setting. *Int Clin Psychopharmacol.* 1997;12(3):175-179.
7. Meehan K, Zhang F, David S, et al. A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. *J Clin Psychopharmacol.* 2001;21(4):389-397.
8. Ghiasi N, Bhansali RK, Marwaha R. Lorazepam. In: *StatPearls.* StatPearls Publishing; 2020.
9. Food and Drug Administration. Drug shortages. https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages. Updated January 29, 2021. Accessed March 26, 2021.
10. 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 March 26, 2021.
11. 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.
12. 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. Survey instrument for pharmacy roundtable prequestionnaire

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

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

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

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

Appendix 3. Survey distribution to professional associations

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

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