Summary Report

Adenosine

Prepared for:

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

Prepared by:

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

November 2021

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

Table of Contents

Table of Tables

Frequently Used Abbreviations

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

INTRODUCTION

This report was created to assist the United States Food and Drug Administration (FDA) in their evaluation of the use of adenosine (UNII code: K72T3FS567), 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 adenosine 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 adenosine has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of adenosine 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

Adenosine was nominated for inclusion on the 503B Bulks List by Pentec Health and the Outsourcing Facilities Association (OFA). Adenosine was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Adenosine was nominated for use as an intravenous injection in doses that differ from the commercially available product (for example, 5 mg/mL), as an intrathecal injection in concentrations up to 3 mg/mL, and as an oral product for:

- Abnormal heartbeat or cardiac arrhythmias such as paroxysmal supraventricular tachycardia (PSVT)
- Stable narrow-complex supraventricular tachycardia (SVT)
- Regular monomorphic wide-complex tachycardia
- Cardiac stress test
- Weight-loss treatment
- Complex pain conditions such as hyperalgesia, allodynia, and chronic neuropathic pain

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of adenosine.[6-9]

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

- As with any drug product, patients respond differently. The compounded product may be the only product to effectively treat the indication for which it is intended.
- The FDA-approved product is only available for intravenous injection at one strength. It may be necessary to compound doses more concentrated than the FDA-approved drug.
- Adenosine is not available as an oral product.
- Adenosine is used in combination with other products such as methionine, inositol, choline, methylcobalamin, and levocarnitine.
- Practitioners often prescribe doses that require higher strengths or concentrations than those available in FDA-approved products or use in combinations with other medications.
- Adenosine's FDA-approved labeling says it is for single-use only. If the FDA-approved vials were used for compounding and the vial was punctured a second time or the vial's contents were

used for more than one patient, then the compounding pharmacy would be using the product off-label.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of adenosine products in the US and around the world. The World Health Organization (WHO), the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for adenosine; name variations of adenosine 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 adenosine. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive two search strategies for both Ovid MEDLINE and Embase. The first search strategy used a combination of controlled vocabulary terms and keywords to describe three concepts: adenosine; oral, epidural, or intrathecal administration; and therapeutic or diagnostic use. The second search strategy also used a combination of controlled vocabulary terms and keywords to describe three concepts: adenosine; intravenous administration; and substances nominated for use in combination with (refer to Appendix 1 for full search strategies). A literature review was not conducted on the use of single-agent intravenous adenosine products due to the availability of an FDA-approved single-agent adenosine product for intravenous administration. Results were limited to human studies in English language. Searches were conducted on August 22, 2020. In addition, the ECRI Guidelines Trust® repository was searched on August 22, 2020 for clinical practice guidelines that recommended the use of adenosine and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.2 (Clarivate), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which adenosine was used in the nominated dosage form; ROA; and/or combination product to diagnose, prevent or treat the nominated disease or condition; or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if adenosine was used as: an FDA-approved product in the nominated dosage form, ROA, or combination; a dosage form, ROA, or combination that was not nominated; or an unspecified dosage form or ROA. Studies in which adenosine was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names, article title, journal, year of publication, country, study type, historical use of adenosine, setting, total number of patients, number of patients who received adenosine, patient population, indication for use of adenosine, dosage form and strength, dose, ROA, frequency and duration of therapy, use of adenosine in a combination product, use and formulation of adenosine in a compounded product, use of adenosine compared to FDA-approved drugs or other treatments, outcome measures, and authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances adenosine 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 adenosine. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

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

Survey

A survey was distributed to the members of professional medical associations to determine the use of adenosine 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

- Adenosine is available as an FDA-approved product in the nominated dosage form and ROA.
- Adenosine is available as a topical OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for adenosine.
- Adenosine 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[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Adenosine	3 mg/mL	Injectable, Solution	Injection, Intravenous	Prescription	8/29/2013

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

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Adenosine	3-5 mg/mL	Injection, Solution, Solution for injection	Injection/infusion, Injectable, Intravenous, Intravenous bolus, Intravenous infusion	Abu Dhabi	Active	–
				Australia	S4 – Prescription only medicine	7/19/1996
				Belgium	Medical prescription	5/18/1995
				Canada	Prescription	12/31/1994
				Hong Kong	Prescription only	6/04/1998
				Ireland	Prescription-only non-renewable	6/16/1994
				Latvia	Prescription	10/01/2010
				Namibia	–	3/14/2005
				New Zealand	Prescription	12/15/1994
				Saudi Arabia	Prescription	–
				UK	Prescription-only medication	5/03/2010

Abbreviation: –, not provided.

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

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

Results of literature review

Study selection

Database searches yielded 4745 references; 4 additional references were identified from searching ECRI Guidelines Trust® and the published article from abstract. After duplicates were removed, 3416 titles and abstracts were screened. After screening, the full text of 202 articles was reviewed. Finally, 8 studies were included. One hundred ninety-four studies were excluded for the following reasons: wrong study design (133 studies), FDA-approved dosage form or ROA (29), unspecified dosage form or ROA (22), wrong substance (4), dosage form or ROA not nominated (2), unable to obtain full text (2), adenosine not used clinically (1), and language other than English (1).

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

Characteristics of included studies

The 8 included studies were published between 2000 and 2015. There were 8 experimental studies conducted in the following countries: India, Sweden, and US.

A total of 359 patients participated in the # included studies. The number of patients in each study ranged from 7 to 90.

Outcome measures differed among the included studies and included: duration of pain relief, pain intensity, reduction of areas of allodynia and hyperalgesia, requirement for rescue analgesia, sedation, time to first rescue analgesia.

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

Use of adenosine

Two hundred forty-seven patients received adenosine for analgesia, administered as a single intrathecal injection in doses ranging from 0.25-2 mg.

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

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

In 4 studies, the authors' concluding statement did not recommend the use of intrathecal adenosine for analgesia.[10-13] There were 3 studies where the authors concluded that further studies were necessary for the use of intrathecal adenosine for analgesia.[7,8,14] One study did not provide a conclusive recommendation for the use of intrathecal adenosine for analgesia.[15] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

Additional were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of adenosine.

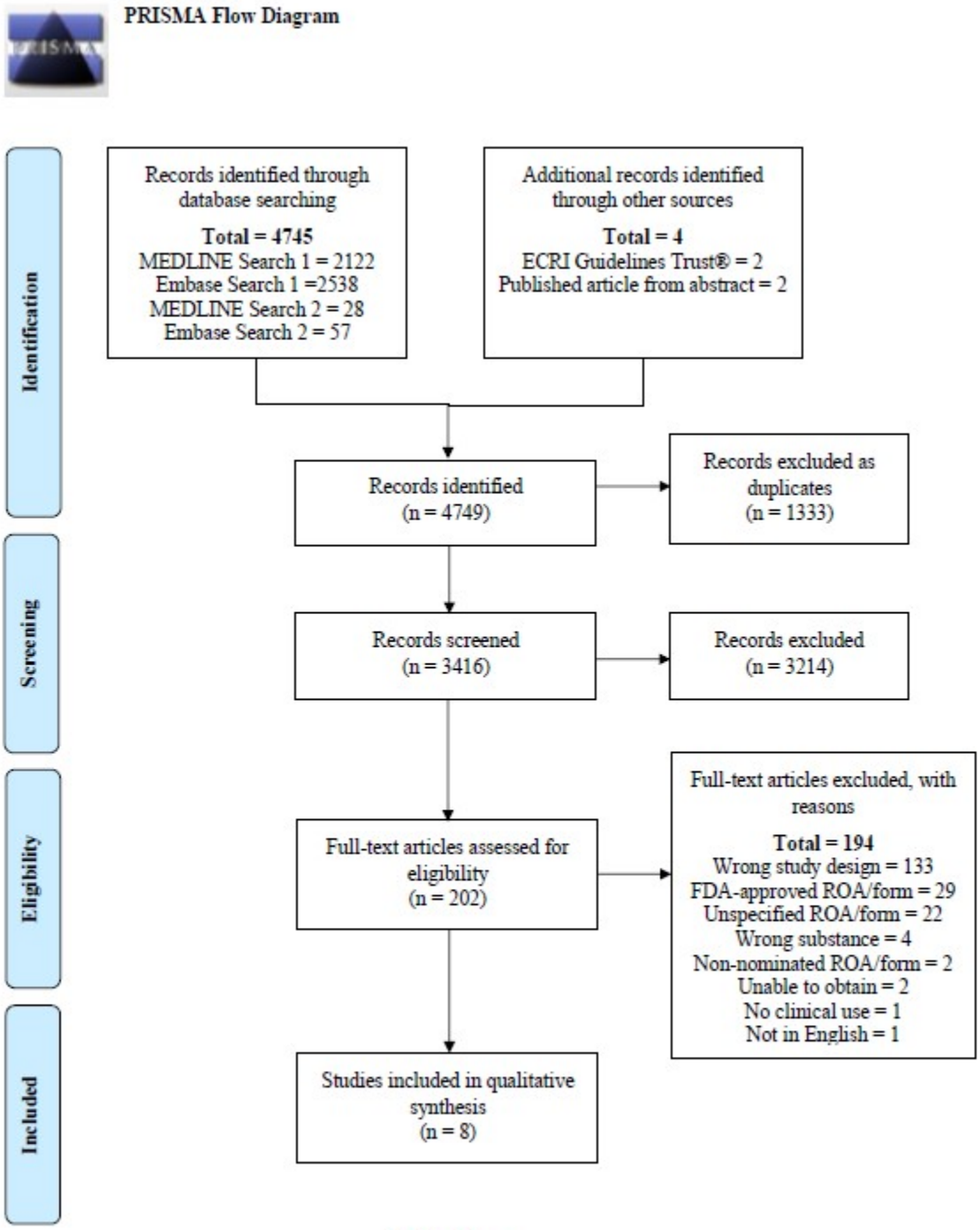
Several studies were identified in the literature review where oral adenosine was used as a supplement for athletic performance and muscular strength in male patients or to treat subacute lower back pain, primary varicose veins, X-linked recessive muscular dystrophy, and acute intermittent porphyria; these studies were excluded due to the use of salt forms adenosine 5'-triphosphate, adenosine-5-

monophosphate, and heptaminol adenosine phosphate.[16-23] The reason they were excluded relates to a 1998 notice from the FDA where adenosine phosphate was withdrawn due to the fact that it "was determined to be neither safe nor effective for its intended uses as a vasodilator and an anti-inflammatory. FDA directed the removal of these drug products from the market in 1973."[24] More recently in 2016, the FDA released another notice addressing individual salt forms of adenosine phosphate – adenosine 5'-monophosphate (AMP), adenosine 5'-diphosphate (ADP), and adenosine 5'-triphosphate (ATP) – and their use in bulk compounding.[25] The FDA came to the conclusion that the substances did not satisfy the requirements for a bulk drug substance to be used in compounding and "would be ineligible for the exemptions provided under either section 503A or section 503B."[25]

There was a 2018 randomized clinical trial looking at the use of epidural adenosine for cancer-related neuropathic pain.[26] The authors concluded that bolus administration of epidural adenosine 50 mcg/kg "is not effective in reducing neuropathic pain in patients with primitive neuroectodermal tumors."[26] However, the authors did comment that adding adenosine to epidural ropivacaine "shows a significant superiority in reducing nausea and vomiting," but that it requires further clinical trials.[26]

In 2020, an open-label one-arm pilot trial was conducted in Iran to investigate the use of intrathecal adenosine in patients with neuropathic pain after lumbar discectomy.[27] The authors commented at the beginning that intravenous adenosine has resulted in reduced analgesic requirements for surgical procedures with the added benefit of "[limiting] systolic blood pressure fluctuations cause by painful stimuli during a surgery."[27] In this study, 40 patients received 1000 mcg of intrathecal adenosine and were observed for 48 hours after injection.[27] The authors' concluding statement was that "intrathecal injection of adenosine is a safe and effective method for post-operative pain management after uni-level disk surgeries;" however, they also noted several limitations to their study.[27] These limitations included lack of a control group, relying on patient reporting regarding their consumption of analgesics based on number of pills taken, and a confounding factor regarding the "daily job which could directly impact pain sensation severity reported by the patient."[27]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	**Number of Studies**
Descriptive	0
Observational	0
Experimental[7,8,10-15]	8

Table 4. Number of studies by country

Country	**Number of Studies**
India[10,13]	2
Sweden[11,12]	2
US[7,8,14,15]	4
	Total US: 4 Total Non-US Countries: 4

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication: Analgesia					
Eisenach et al, 2002, US[7]	Open-label study Randomized, double-blind manner	5 Healthy volunteers to confirm stability of new method of capsaicin-induced hypersensitivity (40%, range 31-45 y) 30 Healthy volunteers who received treatment after capsaicin established areas of allodynia and hyperalgesia (43.3%, mean 30 y ± 1.5)	Intrathecal saline followed by intravenous administration of: • Saline (5) • Aminophylline (5) Intrathecal adenosine 0.5 mg followed by intravenous administration of: • Saline (5) • Aminophylline (5) Intrathecal adenosine 2 mg followed by intravenous administration of either: • Saline (5) • Aminophylline (5)	Reduction of areas of allodynia and hyperalgesia	"In summary, intrathecal adenosine, 0.5 and 2 mg, reduces areas of mechanical hyperalgesia and allodynia following the application of heat and topical capsaicin in volunteers, with no differences in efficacy between doses. Side effects, however, were more common with the larger dose than with saline control. These data suggest that doses of intrathecal adenosine of 0.5 mg or less should be investigated for the treatment of pain."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Eisenach et al, 2002, US[14]	Open-label, dose-escalating trial Double-blind, placebo-controlled trial	25 Healthy volunteers receiving treatment after acute thermal nociception (60%, mean 33 y ± 1.4) 40 Healthy volunteers receiving treatment for capsaicin-induced hypersensitivity (52.5%, mean 31 y ± 1.1)	Volunteers for the dose-escalating trial received intrathecal adenosine at doses of either: • 0.25 mg (5) • 1 mg (5) • 1.5 mg (5) • 2 mg (5) Volunteers for double-blind, placebo-controlled trial received either: • Saline (10) • Intrathecal adenosine (30)	Pain, reduction of mechanical hyperalgesia and allodynia	"In summary, intrathecal adenosine reduces mechanical allodynia in humans induced acutely by intradermal capsaicin injection, with a remarkably long time course, much longer than its residence time in CSF. In contrast, there is no apparent effect of intrathecal adenosine on acute noxious thermal stimulation. These data are consistent with studies in animals of intrathecal adenosine in acute nociception and chronic nerve injury and with uncontrolled trials in volunteers and patients in Sweden with a different formulation of adenosine. They suggest that further controlled clinical trials of intrathecal adenosine to reduce hypersensitivity phenomena after acute injury, such as surgery, or chronic injury, such as in some patients with neuropathic pain, are warranted."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Eisenach et al, 2003, US[8]	Prospective, double-blind, randomized cross-over design	7 Patients with chronic neuropathic pain associated with a defined area of allodynia and an area of hyperalgesia (42.9%, mean 37 y ± 6)	• Intrathecal adenosine (7) • Intravenous adenosine (7)	Reduction of areas of allodynia and hyperalgesia	"In conclusion, intrathecal, but not intravenous adenosine produced a modest reduction in some aspects of hypersensitivity, including pain from stimulation in the area of hyperalgesia and reduced area of allodynia in patients with neuropathic pain. Intrathecal and intravenous adenosine had no effect on ongoing pain. These data suggest that intrathecal adenosine does reduce hypersensitivity to mechanical stimulation in patients with neuropathic pain, but is unlikely to be useful as a sole analgesic. Further studies examining the clinical relevance of laboratory studies demonstrating powerful interactions between intrathecal adenosine and clonidine or morphine appear warranted."
Ghai et al, 2011, India[10]	Randomized in a double-blind prospective manner	75 Patients scheduled for vaginal hysterectomy (0%, range 30-65 y)	Intrathecal bupivacaine with: • Adenosine 500 mcg (25) • Adenosine 1000 mcg (25) • Normal saline (25)	Time to first rescue analgesia, total dose of fentanyl needed	"Intrathecal adenosine does not affect the postoperative analgesic requirement when administered with hyperbaric bupivacaine."
Rane et al, 2003, Sweden[11]	Double-blind, placebo-controlled randomized study	25 Patients requesting labor analgesia (0%, age not specified)	Intrathecal administration of: • Adenosine and sufentanil (13) • Sufentanil (12)	Pain intensity, duration of pain relief	"Adding 500 mcg of adenosine to 10 mcg of sufentanil could not provide any prolongation of labour pain relief."
Rane et al, 2000, Sweden[12]	Placebo-controlled, randomized, double-blind study	40 Patients scheduled for elective hysterectomy (0%, range 37-66 y)	• Intrathecal adenosine (20) • Placebo (20)	Pain scores, cetobemidone requirement	"IT [Intrathecal] adenosine did not influence the requirement of anaesthetic drug or postoperative analgesics after hysterectomy."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Rauck et al, 2015, US[15]	Double-blind crossover study	22 Patients with complex regional pain syndrome (40.9%, mean 44 y ± 10)	• Intrathecal adenosine (22) • Intrathecal clonidine (22)	Pain reduction	"Both intrathecal clonidine and adenosine acutely inhibit experimentally induced and clinical hypersensitivity in patients with chronic regional pain syndrome. Although these drugs do not differ in analgesia by the primary outcome measure, their difference in effect on pain scores over time and lack of correlation between effect on pain and hypersensitivity suggest that analgesia does not parallel antihyperalgesia with these treatments."
Sharma et al, 2006, India[13]	–	90 Patients undergoing elective abdominal hysterectomy • Early adenosine (0%, mean 38.9 y ± 10.0) • Late adenosine (0%, mean 41.5 y ± 7.9) • Control (0%, mean 39.5 y ± 8.7)	• Control (30) Intrathecal adenosine administered either: • Early: 30 minutes before anesthesia induction (30) • Late: before reversal of neuromuscular blockade (30)	Pain and sedation scores, time to first rescue analgesic, total morphine requirement	"While the literature supports the role of intrathecal adenosine to relieve experimental and neuropathic pain, the efficacy of this drug to relieve postoperative pain remains unproven. The results of the present study failed to show any effect of intrathecal adenosine administered in dose of 1000 mcg, pre-emptively or after surgery in patients undergoing abdominal hysterectomy. Mechanisms of action of adenosine for pain relief need to be further explored."

Abbreviation: –, not provided.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Analgesia[7,8,14,15]	0.25-2 mg	0.125-2 mg/mL	–	Intrathecal	Once

Abbreviations: –, not provided.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Analgesia[10-13]	0.5-1 mg	0.156-1 mg/mL	–	Intrathecal	Once
			Solution		

Abbreviations: –, not provided.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	The nominations identified the need for combination products. However, no information was provided regarding the specific combinations desired.	0

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

One hundred ninety-nine SMEs were contacted for interviews; 63 agreed to be interviewed, and 136 declined or failed to respond to the interview request. Three SMEs discussed adenosine. Amongst these 3 SMEs, there was 1 medical doctor, 1 naturopathic doctor, and 1 nurse practitioner. The SMEs specialized and/or were board-certified in naturopathic medicine, oncology, and primary care, working in academic medical institutions, consulting, and retired. The SMEs had been in practice for 12 to 30 years.

Only 1 of the SMEs had experience using adenosine, however, this was only as the IV formulation in the context of a cardiac stress test. Typically, for a cardiac stress test a patient is asked to run on a treadmill, but if they are unable to do this a medication, like adenosine, is administered that will speed up the heart and simulate the same stress.

One of the SMEs commented on the use of adenosine in pain. There are reports that adenosine reduces irritation and transmission of painful stimuli through the nerves. As a result, it can be administered "into the spinal cord for people that have herniated discs and painful spinal conditions, and that seems like it's got some promise to it." The SME stated that they "like the idea of having another tool that we can use instead of opioids to help people with these pain conditions."

Two of the SMEs commented on the use of adenosine as part of a weight management program. One SME stated that adenosine is typically used in combination with methionine, inositol, choline, methylcobalamin, and levocarnitine as part of a weight management program as a metabolism stimulant. The carnitine would "speed fat uptake into the mitochondria," the methionine, inositol, and choline (MIC) is used as "metabolic support for the metabolism at the level of the liver," and the methylcobalamin and the adenosine are methyl donors to act as a metabolism stimulant. The MIC is compounded into 1 vial and then the carnitine, adenosine, and methylcobalamin are compounded as separate vials. Some clinics administer them as a multi-component intramuscular injection while others dilute them and administer as a slow IV infusion. The injections are done once weekly "during their initiation part where they're changing their diet." One SME commented that they have seen each of these medications administered as an oral product, except for the adenosine, stating "I think the consideration with adenosine orally, is I'm not sure if it makes it past the stomach acid very well."

One SME has seen patients that have benefited from this product when combined with diet and exercise. However, another SME stated "I've always been rather skeptical about any medication for weight loss in terms of, this may help you for three months, but where are you going to be 20 years from now? When I treated patients, I would tell them, 'Whatever you're going to do to lose weight has to be something you're willing to do forever.' So, whether it's a dramatically radicalized diet or some expensive medication, or even just a cheap medicine that you're going to take for a brief period of time for rapid weight loss and then not do it forever, you're wasting your time and your money on that nonsense." Regarding potential unintended cardiac effects from using adenosine, 1 SME said that "the doses are on the very low end for adenosine" and so "the number of people who've had cardiovascular issues from those low doses is extremely low." Another SME said that "adenosine supplementation as part of a weight loss program seem to be reasonably safe and effective, as effective as any weight loss thing that doesn't involve adopting a healthier lifestyle" continuing that "as long as people take it in recommended doses, it's a pretty natural substance, it's not going to be terribly harmful."

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 with which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented that "we look at the impact

that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we're going to look to potentially move out." Another participant stated that, while they do not obtain a lot of products from outsourcing facilities, "when we do purchase from 503Bs, typically it would be if we just don't have the capacity to keep up with what the demand is." One participant also commented that they will obtain labor-intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The coronavirus disease 2019 (COVID-19) pandemic has also impacted the operations of hospitals, as noted by one participant who stated that "it's just really high volume, and the bigger the hospital, the higher the volume, especially when you have one disease state in half of your hospital" and another who expressed that "without 503B, we would've been in significant trouble." One participant commented that "even though the number might be small [percent of products obtained from outsourcing facilities], some of the reasoning is quite critical, and the amount of time that it saves is very significant for beyond what we're able to do and when." Additionally, challenges with recruiting and retaining pharmacy technicians impact decision-making, with one participant stating "it is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready-to-use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing."

In addition to the evaluation of the workload on pharmacy staff, the type and capabilities of the facility also impacted the decision-making process. One participant commented that they do not have an established cleanroom and therefore perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use date that can be assigned to these products and, as the participant stated, "We obviously need to provide product with much [more] extensive beyond-use dating than we can provide." Several participants also commented that they do not perform high-risk compounding in-house and therefore, all of these products are outsourced. There are challenges with midsize hospitals being able "to operationalize testing compounds we make for extended stability." One participant stated, "We might make our own syringes if we could get extended dating, but I believe my operations colleagues don't always know how to do this and adhere to the letter of the law."

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

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products used. However, the products used in a facility are often developed in-house over decades based on physician and nurse requests, and more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, "these practices had evolved somewhat disparately. Even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines." This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, "I

think we made 9 different epidural concentrations, all driven by anesthesia, and they want what they want, and 503Bs may not offer that. No one else in the country is buying that same concentration; a 503B isn't going to go through the expense of adding that to their product list." The participant also said that "similar with the ADCs [automated dispensing cabinets], we've run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, 'no, we can't have it, and that's too big, it won't fit, we want it in this format' and then we're stuck again because there's no 503B offering a format during that shortage that fits where it needs to go. Then we're stuck in sourcing." Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that "3% saline, for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We're either going to draw that out or we're sending it to the ER with stickers all over it saying only give 150 [mL]." The participant continued that "it would be great if the FDA could look at the size of the container that they're approving and whether that's a realistic dose: is it a unit dose, or isn't it?"

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

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

A few participants commented on the need for preservative-free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative-containing product. So, there is a need for this product to be compounded from API as a preservative-free product. One participant stated that "if there's not a preservative-free containing option, it really should be something that should be able to be compounded from bulk . . . especially for the pediatric patient population." However, another participant from a children's hospital said that they have never needed to use an outsourcing facility for preservative-free

products. Preservative-free is also an issue for ophthalmic products; however, one participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing facilities but are not able to, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products, but when they reviewed the facilities, they did not pass their internal quality standards; one facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams due to the potential cross-reactivity in patients with allergies. One participant stated that there are some cephalosporins they would like to obtain from an outsourcing facility but cannot because "they would have to build a separate cleanroom with a dedicated HVAC [heating, ventilation, and air conditioning], so you're talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn't there." Another participant stated that the concentrations required for ophthalmic antibiotics are not available, but the labor and risk of compounding these products in-house are not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. LET (lidocaine-epinephrine-tetracaine) gel, for use as a topical anesthetic, was the most commonly obtained product along with buffered lidocaine to put in J-Tips. Another participant stated that they obtain diclofenac suppositories from an outsourcing facility due to the high cost of indomethacin suppositories. One participant commented that most of the products they outsource are nonsterile products, generally for oral or topical administration due to a lack of commercially available products. The participant stated that they purchase low-dose naltrexone for oral use in patients with refractory fibromyalgia and ketamine troches for patients with chronic pain. The participant continued that while the evidence does not support many of the ingredients used in topical pain products, "However, there are select patients. It's very rare that taking that cream away from them actually causes more harm than good." A few participants commented that there is a gap in the market for nonsterile products, with one stating, "I think that there is a large opportunity for more nonsterile products to be produced by 503Bs." Another stated that as their facility grows and acquires more outpatient clinics, they receive a lot of questions regarding obtaining products for office use. The participant noted that they often have to refer these clinics to outsourcing facilities but stated "there's not many 503Bs [that] are doing the nonsterile for clinic use." As a result, the inpatient pharmacy is often asked to take on this role but "you don't have the space or the staff to do that."

Based on the responses to the prequestionnaire (refer to *Results of survey*), participants were asked questions regarding specific products obtained from outsourcing facilities. Several participants reported using alum (aluminum potassium) as a bladder irrigation for hemorrhagic cystitis refractory to other treatment options. Participants commented that this is high-risk compounding; they purchase alum from an outsourcing facility because they do not perform high-risk compounding in their facility. One participant commented that their policy states that high-risk compounding is not allowed except for alum. This participant wanted to move away from compounding alum in-house and stated that the addition of aluminum potassium to the bulks list might allow this to happen. Another participant had compounded alum in-house from nonsterile ingredients; however, there had been challenges with crystallization after storage. A few participants commented that there is a sterile alum powder available, which they purchase to compound in-house. One participant had concerns regarding this powder, stating that "I've talked to that company, but I've had some concerns for them because they don't sell it as a drug. The owner was selling you a chemical, we're selling you a bulk API. It's just sterile. They were fuzzy and I never followed up, but when I asked about their process for verifying the sterility, as you would with a sterile product—we do USP <71> Sterility Testing—they couldn't really give me an answer. They just say they

tested for sterility." The participants commented that alum is only needed a few times a year. However, as one participant observed, "When you need it, it's an emergency," and another noted that it "is a challenge for anybody who has cyclophosphamide-induced hemorrhagic cystitis." As a result, one participant maintains a small inventory of alum product that is purchased from an outsourcing facility but "more times than not, they go unused and expire." Another stated that they do not keep it in stock because there is a minimum purchase and there are only a few cases a year for which they need to use alum. The participant had it stat shipped when needed. Another participant stated that "we had a meeting with the head of urology who was baffled, why they're even ordering it. He was like, 'this is . . . old, really old. I don't even know why we're using it' and basically approved for us to not even make it anymore for now."

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

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution in patients undergoing dialysis, with one commenting that "our nephrologists like it in place of heparin for some patients to keep the ports patent or so they don't have to go to alteplase or some of the other drugs." There is a commercially available product; however, it is only available as a 500 mL bag and the dose needed is typically less than 30 mL. If the syringes are prepared in-house, then the beyond-use date is limited to 12 to 24 hours depending on storage, which results in waste.

One participant stated that they obtain papaverine from outsourcing facilities for use in urology as Bimix (papaverine/phentolamine) and Trimix (papaverine/phentolamine/alprostadil).

While none of the participants obtained sodium phosphate or aspartic acid from outsourcing facilities for use in cardioplegic solutions, a few commented that they do obtain cardioplegic solutions from outsourcing facilities. The del Nido formulation was the product most commonly obtained. One participant commented that they compound this formulation in-house because the outsourcing facilities did not offer the volume needed at their institution. Another participant commented that while they do obtain the del Nido formulation from an outsourcing facility, they also compound a proprietary formulation in-house. This participant observed that "it is complicated to do in-house. We do it on a Baxa 1200 or 2400, either one, compounder. Then we send it up to [*sic*] for pH and potassium testing. Obviously, then we're confined to <797> beyond-use dates versus longer beyond-use dates that we get from the 503B." Another participant commented that cardioplegic solutions are managed by the perfusion department, not pharmacy, and they use del Nido solution as well as 3 other formulations.

The participants also discussed challenges with utilizing outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because "it just hasn't been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to. . . . It just isn't worth the dating that they gave us or can give us." Another commented that they obtain very little product from outsourcing facilities due to "the amount of work for vetting and continually validating

quality of these 503B outsourcing facilities." The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that "[t]raditionally, we've found 503Bs to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed, but we've had some other smaller 503Bs where we've had agreements for certain products to take it off our plate, and then lo and behold they're shut down, or closed, or whatever it may be." Minimum purchase amounts were also reported as a concern with one participant stating that "what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients." Another challenge was related to outsourcing facilities utilizing API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration places on the quantity that can be produced. The participant stated that "they [outsourcing facilities] want to buy the product that we're trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don't end up with a shortage year after year after year and then chasing our tail. Also, we may actually want to tell 503Bs they can't buy those products or that they're limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products because it actually induces the shortage in many ways."

Results of survey

One person responded to the survey distributed via professional medical associations and available on the project website (refer to Table 11 for respondent characteristics).

Among respondents, 1 (100%) used adenosine. The respondent did not provide information regarding the ROA/dosage form, indications, use in combination with additional APIs, or whether a compounded formulation or FDA-approved product was used.

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) using outsourcing facilities to obtain drug products, 4 (9%) did not use outsourcing facilities, and 4 (9%) did not respond to this question.

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

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

Table 11. Characteristics of survey respondents

No survey respondents provided this information

Table 12. Conditions for which adenosine prescribed or administered

No survey respondents provided this information

Table 13. Reasons for using compounded adenosine

No survey respondents provided this information

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

No survey respondents provided this information

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 allowed to select multiple facilities.
[b]Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, 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 on-site compounding facility	1
On-site compounding facility not equipped to compound all necessary products	19
Other[b]	8

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

Adenosine was nominated for inclusion on the 503B Bulks List as an oral product, an IV injection, and an intrathecal injection to treat a variety of conditions. Adenosine 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.

From the literature review, 8 studies were included. Adenosine was used for analgesia as an intrathecal injection in doses ranging from 0.25-2 mg. The studies either did not recommend the use of intrathecal adenosine for analgesia or stated that further studies were necessary for the use of intrathecal adenosine for analgesia. No studies were found in which adenosine was used as an oral product.

From the interviews, 3 SMEs discussed adenosine. Only 1 SME had experience using adenosine, but this was as the IV formulation as part of a cardiac stress test. One SME commented that there are promising reports regarding the intrathecal use of adenosine for the treatment of pain and that this could be a useful alternative to opioids when managing patients with chronic pain. Two SMEs stated that adenosine can be useful as part of a weight management program with 1 SME stating that adenosine was typically used in combination with MIC, levocarnitine, and methylcobalamin.

From the survey responses, 1 out of 1 respondent used adenosine. The respondent did not provide any information regarding the dosage form/ROA, indication, or whether a compounded formulation or FDA-approved product was used. From the prequestionnaire, 2 respondents obtained adenosine from a 503B outsourcing facility.

REFERENCES

1. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. *International Journal of Social Research Methodology: Theory and Practice.* 2005;8(1):19-32.
2. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol.* 2014;67(12):1291-1294.
3. Levac D, Colquhoun H, O'Brien KK. Scoping studies: Advancing the methodology. *Implementation Science.* 2010;5(1).
4. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *International Journal of Evidence-Based Healthcare.* 2015;13(3):141-146.
5. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol.* 2018;18(1):143-143.
6. Belfrage M, Segerdahl M, Arnér S, Sollevi A. The safety and efficacy of intrathecal adenosine in patients with chronic neuropathic pain. *Anesth Analg.* 1999;89(1):136-142.
7. Eisenach JC, Curry R, Hood DD. Dose response of intrathecal adenosine in experimental pain and allodynia. *Anesthesiology.* 2002;97(4):938-942.
8. Eisenach JC, Rauck RL, Curry R. Intrathecal, but not intravenous adenosine reduces allodynia in patients with neuropathic pain. *Pain.* 2003;105(1-2):65-70.
9. Rane K, Segerdahl M, Goiny M, Sollevi A. Intrathecal adenosine administration: a phase 1 clinical safety study in healthy volunteers, with additional evaluation of its influence on sensory thresholds and experimental pain. *Anesthesiology.* 1998;89(5):1108-1115; discussion 1109A.
10. Ghai A, Hooda S, Saxena S, Garg N, Wadhera R. Addition of adenosine to hyperbaric bupivacaine in spinal anaesthesia does not prolong postoperative analgesia in vaginal hysterectomy. *Southern African Journal of Anaesthesia and Analgesia.* 2011;17(4):288-292.
11. Rane K, Sollevi A, Segerdahl M. A randomised double-blind evaluation of adenosine as adjunct to sufentanil in spinal labour analgesia. *Acta Anaesthesiologica Scandinavica.* 2003;47(5):601-603.
12. Rane K, Sollevi A, Segerdahl M. Intrathecal adenosine administration in abdominal hysterectomy lacks analgesic effect. *Acta Anaesthesiologica Scandinavica.* 2000;44(7):868-872.
13. Sharma M, Mohta M, Chawla R. Efficacy of intrathecal adenosine for postoperative pain relief. *European Journal of Anaesthesiology.* 2006;23(6):449-453.
14. Eisenach JC, Hood DD, Curry R. Preliminary efficacy assessment of intrathecal injection of an American formulation of adenosine in humans. *Anesthesiology.* 2002;96(1):29-34.
15. Rauck RL, North J, Eisenach JC. Intrathecal clonidine and adenosine: effects on pain and sensory processing in patients with chronic regional pain syndrome. *Pain.* 2015;156(1):88-95.
16. Bannwarth B, Allaert FA, Avouac B, Rossignol M, Rozenberg S, Valat JP. A randomized, double-blind, placebo controlled triphosphate in study of oral adenosine subacute low back pain. *Journal of Rheumatology.* 2005;32(6):1114-1117.
17. Schmidt C, Gavoille R, Perez P, Schmitt J. Double-blind plethysmographic study of venous effects of heptaminol adenosine phosphate in patients with primary varicose veins. *European Journal of Clinical Pharmacology.* 1989;37(1):37-40.

18. Thomson WHS, Smith I. Effects of oral allopurinol and adenosine 5'-triphosphate in X-linked recessive (Duchenne) muscular dystrophy. *Journal of Clinical Chemistry and Clinical Biochemistry.* 1982;20(6):426-427.

19. Wetterberg L. Treatment of acute intermittent porphyria with adenosine-5-monophosphate: a long-term double-blind study. *Journal of Clinical Pharmacology & the Journal of New Drugs.* 1970;10(3):199-202.

20. Freitas MC, Cholewa JM, Gerosa-Neto J, et al. A single dose of oral ATP supplementation improves performance and physiological response during lower body resistance exercise in recreational resistance-trained males. *Journal of Strength & Conditioning Research.* 2019;33(12):3345-3352.

21. Janse Van Rensburg C, Tabane C, Grant R, Wood P. Increased physical performance by using a nutritional supplement: Fact or fantasy? *Journal of Science and Medicine in Sport.* 2010;13:e84-e85.

22. Jordan AN, Jurca R, Abraham EH, et al. Effects of oral ATP supplementation on anaerobic power and muscular strength. *Medicine & Science in Sports & Exercise.* 2004;36(6):983-990.

23. Wilson JM, Joy JM, Lowery RP, et al. Effects of oral adenosine-5′-triphosphate supplementation on athletic performance, skeletal muscle hypertrophy and recovery in resistance-trained men. *Nutrition and Metabolism.* 2013;10(1).

24. Schultz WB. List of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness. *Federal Register.* 1998;63(195):54082-54089.

25. Kux L. Additions and modifications to the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness. *Federal Register.* 2016;81(195):69668-69677.

26. Gharehdaghi FA, Shahverdi E, Mofrad NN, Faranoush M, Ebadi A. Does a single dose of adenosine in epidural space reduce cancer-related neuropathic pain? A randomized clinical trial. *International Journal of Cancer Management.* 2018;11(5).

27. Aghamohammadi D, Eydi M, Pishgahi A, Esmaeilinejad A, Dolatkhah N. Pilot prospective open-label one-arm trial investigating intrathecal Adenosine in neuropathic pain after lumbar discectomy. *BMC Research Notes.* 2020;13(1):284.

APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy 1

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to August 21, 2020
- Date last searched: August 22, 2020
- Limits: Humans (search hedge); English language
- Number of results: 2122

1	adenosine/	29600
2	adenosine triphosphate/	102843
3	adenin$ riboside.tw.	18
4	adenosin$.tw.	111643
5	or/1-4	204076
6	administration, oral/	142931
7	infusions, spinal/	158
8	exp injections, spinal/	16113
9	epidural space/	4510
10	oral$.tw.	672954
11	spinal$.tw.	268587
12	intraspinal$.tw.	5053
13	epidural$.tw.	42213
14	extradural$.tw.	6763
15	extra dural$.tw.	142
16	peridural$.tw.	2065
17	peri dural$.tw.	6
18	caudal$.tw.	45715
19	intracaudal$.tw.	11
20	arachnoid$.tw.	8160

21	subarachnoid$.tw.	35724
22	intrathecal$.tw.	23841
23	intra thecal$.tw.	76
24	or/6-23	1096859
25	drug therapy/	30568
26	exp diagnosis/	8550153
27	de.fs.	2991180
28	dt.fs.	2228353
29	ad.fs.	1416237
30	tu.fs.	2227335
31	di.fs.	2570469
32	therap$.tw.	2794553
33	treat$.tw.	5519046
34	diagnos$.tw.	2474194
35	or/25-34	16213296
36	and/5,24,35	4545
37	exp animals/ not humans/	4727457
38	36 not 37	2216
39	limit 38 to english language	2122

MEDLINE search strategy 2

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to August 21, 2020
- Date last searched: August 22, 2020
- Limits: Humans (search hedge); English language
- Number of results: 28

1	adenosine/	29600
2	adenosine triphosphate/	102843
3	adenin$ riboside.tw.	18
4	adenosin$.tw.	111643
5	or/1-4	204076
6	exp administration, intravenous/	143154
7	infusions, parenteral/	26252
8	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	12228
9	intravenous$.tw.	340990
10	intra venous$.tw.	576
11	intravascular$.tw.	47839
12	intra vascular$.tw.	304
13	or/6-12	479129
14	exp methionine/	42027
15	levomet?ionin$.tw.	1
16	met?ionin$.tw.	50405
17	racemet?ionin$.tw.	1
18	choline/	18376
19	bilineurin$.tw.	1
20	bioc?olin$.tw.	0
21	cholin$.tw.	103924
22	l?evocholin$.tw.	0

23	vitamin$ j.tw.	0
24	inositol/	7646
25	inosit#n$.tw.	1
26	inositol$.tw.	37305
27	mesoinosi$.tw.	47
28	myoinosi$.tw.	1265
29	mecobalamin$.tw.	142
30	methylcobal$.tw.	750
31	methyl cobal$.tw.	48
32	methylvitamin$ b12.tw.	1
33	methyl vitamin$ b12.tw.	8
34	methylvitamin$ b 12.tw.	0
35	methyl vitamin$ b 12.tw.	1
36	carnitine/	8702
37	carnitin$.tw.	15137
38	levocarnitin$.tw.	149
39	vitamin$ bt.tw.	12
40	or/14-39	235024
41	and/5,13,40	81
42	exp animals/ not humans/	4727457
43	41 not 42	32
44	limit 43 to english language	28

Embase search strategy 1

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: August 22, 2020
- Limits: Humans (search hedge); English language
- Number of results: 2538

1	‘adenosine'/mj	18256
2	‘adenosine triphosphate'/mj	42464
3	‘adenin* riboside':ti,ab,tn	21
4	‘adenosin*':ti,ab,tn	136472
5	#1 OR #2 OR #3 OR #4	169809
6	‘oral drug administration'/de	406190
7	‘intraspinal drug administration'/de	3459
8	‘epidural drug administration'/de	8888
9	‘intrathecal drug administration'/de	20969
10	‘intracaudal drug administration'/de	20
11	‘epidural space'/de	6439
12	‘oral*':ti,ab	967809
13	‘spinal*':ti,ab	370260
14	‘intraspinal*':ti,ab	7003
15	‘epidural*':ti,ab	59712
16	‘extradural*':ti,ab	9117
17	‘extra dural*':ti,ab	242
18	‘peridural*':ti,ab	3002
19	‘peri dural*':ti,ab	12
20	‘caudal*':ti,ab	59199
21	‘intracaudal*':ti,ab	23
22	‘arachnoid*':ti,ab	12337

23	‘subarachnoid*':ti,ab	51021
24	‘intrathecal*':ti,ab	35481
25	‘intra thecal*':ti,ab	242
26	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	1778403
27	‘drug therapy'/de	743829
28	‘diagnostic procedure'/exp	18712066
29	‘drug dose':lnk	625720
30	‘drug administration':lnk	1755726
31	‘drug therapy':lnk	3925759
32	‘diagnosis':lnk	3266955
33	‘therap*':ti,ab	4203915
34	‘treat*':ti,ab	7994023
35	‘diagnos*':ti,ab	3778570
36	#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35	24943491
37	#5 AND #26 AND #36	5371
38	[animals]/lim NOT [humans]/lim	6078040
39	#37 NOT #38	2751
40	#37 NOT #38 AND [english]/lim	2538

Embase search strategy 2

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: August 22, 2020
- Limits: Humans (search hedge); English language
- Number of results: 57

1	‘adenosine'/de	45955
2	‘adenosine triphosphate'/de	158065
3	‘adenin* riboside':ti,ab,tn	21
4	‘adenosin*':ti,ab,tn	136472
5	#1 OR #2 OR #3 OR #4	278163
6	‘parenteral drug administration'/de	2166
7	‘intravascular drug administration'/de	329
8	‘intravenous drug administration'/exp	393245
9	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18347
10	‘intravenous*':ti,ab	491619
11	‘intra venous*':ti,ab	1457
12	‘intravascular*':ti,ab	68771
13	‘intra vascular*':ti,ab	693
14	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	835582
15	‘methionine'/mj	13636
16	‘levomet$ionin*':ti,ab,tn	2
17	‘met$ionin*':ti,ab,tn	60859
18	‘racemet$ionin*':ti,ab,tn	2
19	‘choline'/de	31132
20	‘bilineurin*':ti,ab,tn	1
21	‘bioc$olin*':ti,ab,tn	4
22	‘cholin*':ti,ab,tn	135550

23	‘l$evocholin*':ti,ab,tn	3
24	‘vitamin* j':ti,ab,tn	2
25	‘inositol'/de	13947
26	‘inositen*':ti,ab,tn	1
27	‘inositin*':ti,ab,tn	2
28	‘inositol*':ti,ab,tn	42462
29	‘mesoinosi*':ti,ab,tn	200
30	‘myoinosi*':ti,ab,tn	8266
31	‘mecobalamin'/de	1780
32	‘mecobalamin*':ti,ab,tn	272
33	‘methylcobal*':ti,ab,tn	1037
34	‘methyl cobal*':ti,ab,tn	64
35	‘methylvitamin* b12':ti,ab,tn	0
36	‘methyl vitamin* b12':ti,ab,tn	6
37	‘methylvitamin* b 12':ti,ab,tn	1
38	‘methyl vitamin* b 12':ti,ab,tn	8
39	‘carnitine'/de	16345
40	‘carnitin*':ti,ab,tn	19739
41	‘levocarnitin*':ti,ab,tn	281
42	‘vitamin* bt':ti,ab,tn	17
43	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42	272139
44	#5 AND #14 AND #43	166
45	[animals]/lim NOT [humans]/lim	6078040
46	#44 NOT #45	57

Appendix 2.1. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer adenosine to your patients?
    - Yes
    - No
3. Do you prescribe or administer adenosine by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Intravenous injection
    - Intrathecal injection
    - Oral products
    - None of the above
4. I prescribe or administer adenosine for the following conditions or diseases: (check all that apply)
    - Arrhythmias
    - Cardiac stress test
    - Pain
    - Weight loss
    - Other (please explain) _____
5. I prescribe or administer adenosine in combination with other active pharmaceutical ingredients as a multi-ingredient product.
    - Yes
    - No
6. I prescribe or administer adenosine with my patients as the following: (check all that apply)
    - FDA-approved drug product
    - Compounded drug product
    - Other (please explain) _____
7. I use compounded adenosine 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 adenosine
- Other (please explain) _____

8. Do you stock non-patient-specific compounded adenosine at your practice?
    - Yes
    - No
    - I'm not sure
9. I obtain compounded adenosine 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

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.