Summary Report

Naloxone hydrochloride dihydrate

Prepared for:

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

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

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of naloxone hydrochloride dihydrate (naloxone HCl dihydrate; UNII code: 5Q187997EE), 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 naloxone HCl dihydrate is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how naloxone HCl dihydrate 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 naloxone HCl dihydrate 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 NOMINATION

Naloxone HCl dihydrate was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society.

Naloxone HCl dihydrate was nominated for opioid overdose via a 0.4 mg/mL intrathecal, intramuscular, subcutaneous, and intravenous injection.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of naloxone HCl dihydrate.[6]

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

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

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of naloxone HCl dihydrate products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in 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 naloxone HCl dihydrate; name variations of naloxone HCl dihydrate 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 naloxone HCl dihydrate. 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 two comprehensive search strategies for Ovid MEDLINE and Embase. The first search strategy used a combination of controlled vocabulary terms and keywords to describe three concepts: naloxone HCl dihydrate, epidural or intrathecal administration, and therapeutic use for drug overdose or pain. The second search strategy used a combination of controlled vocabulary terms and keywords to describe two concepts: naloxone HCl dihydrate and migraine (refer to Appendix 1 for full search strategies). The use of naloxone HCl dihydrate for migraines was identified from the National Organization for Rare Disorders. A systematic literature review was not conducted for intramuscular, subcutaneous or intravenous administration because there are FDA-approved products available for these ROAs. Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on March 30, 2020. In addition, the ECRI Guidelines Trust® repository was searched on March 30, 2020 for clinical practice guidelines that recommended the use of naloxone HCl dihydrate and provided sufficient information on dosing and administration.

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

Study selection

Studies in which naloxone HCl dihydrate 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 naloxone HCl dihydrate was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which naloxone HCl dihydrate 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 naloxone HCl dihydrate; setting; total number of patients; number of patients who received naloxone HCl dihydrate; patient population; indication for use of naloxone HCl dihydrate; dosage form and strength; dose; ROA; frequency and duration of therapy; use of naloxone HCl dihydrate in a combination product; use and formulation of naloxone HCl dihydrate in a compounded product; use of naloxone HCl dihydrate compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances naloxone HCl dihydrate was used in a clinical setting. The systematic literature review and indication from the nomination were reviewed to identify the following medical specialties that would potentially use naloxone HCl dihydrate: anesthesiology, emergency medicine and critical care, pain management, psychiatry, and surgery. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and 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 entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of naloxone HCl dihydrate 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 Year 1 were not contacted to distribute the project Year 2 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

- Naloxone HCl dihydrate is available as an FDA-approved product in the nominated dosage form and ROA.
- Naloxone HCl dihydrate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for naloxone HCl.
- Naloxone HCl dihydrate 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]
Naloxone HCl dihydrate	0.4-5 mg/mL	Solution	Injection, intramuscular	Prescription	09/24/1986

Abbreviations: "–", not mentioned.
[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]
Naloxone HCl dihydrate	0.02-1 mg/mL	Solution	Injection, intramuscular, intravenous, subcutaneous	Abu Dhabi	Active	–
				Australia	(S4) Prescription only	08/10/1991
				Belgium	Medical prescription	11/18/2007
				Canada	Prescription	12/31/1995
				Hong Kong	Prescription only medicine	08/18/2000
				Ireland	Pharmacy-only[c]	10/03/1989
				Latvia	Prescription	10/14/1998
				Namibia	–	08/18/2004
				New Zealand	Prescription	10/01/1992
				Saudi Arabia	Prescription	–
				UK	Prescription-only medication	09/04/1990

Abbreviations: "– ", not mentioned.

[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.

[c]Pharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Results of literature review

Study selection

Database searches yielded 1224 references; 2 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 902 titles and abstracts were screened. After screening, the full text of 382 articles was reviewed. Finally, 18 studies were included. Three hundred sixty-four studies were excluded for the following reasons: wrong study design (259 studies); wrong dosage form or ROA (35); FDA-approved dosage form or ROA (25); naloxone HCl dihydrate not used clinically (15); wrong indication (11); naloxone HCl dihydrate used as brand or proprietary product (6); unable to obtain full text (5); language other than English (3); naloxone HCl dihydrate only mentioned briefly (2); wrong substance (2); duplicate study (1).

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

Characteristics of included studies

The 18 included studies were published between 1980 and 2020. There were 9 experimental studies, 5 observational studies, 4 descriptive studies, and 0 clinical practice guidelines. The 18 studies were conducted in the following countries: Canada, France, Iran, and US.

A total of 711,805 patients participated in the 18 included studies. The number of patients in each study ranged from 1 to 442,669.

Outcome measures differed among the included studies and included: resolution of opioid-induced side effects and pain scores.

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

Use of naloxone HCl dihydrate

Four thousand six hundred forty-six patients received naloxone HCl dihydrate as a treatment for opioid reversal, administered in doses ranging from 40 mcg to 13,000 mcg. Duration of treatment ranged from once to 22 hours. Seventy-five patients received naloxone HCl dihydrate as an experimental treatment for pain management, administered as 20 mcg intrathecally once.

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

Naloxone HCl dihydrate was not used as a compounded product, nor was it used in a combination product.

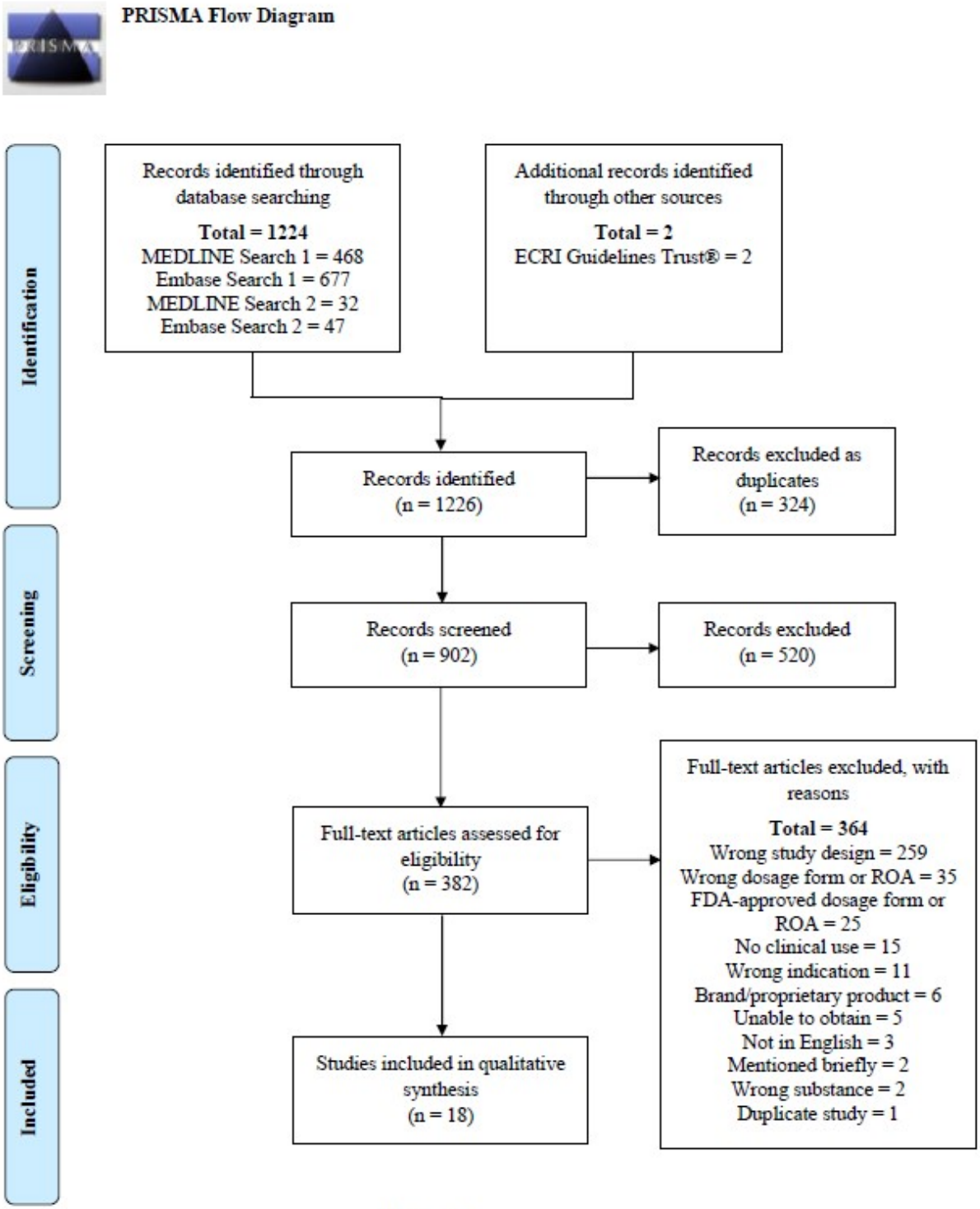
In 1 study, the authors' concluding statement recommended the use of naloxone HCl dihydrate for opioid reversal.[7] In 1 study, the authors concluded that the use of naloxone HCl dihydrate was not recommended for the treatment of pain.[8] In 1 study, the authors concluded that the use of naloxone HCl dihydrate needed further research for the treatment of pain.[9] In 15 studies, the authors conclusion was not relevant to naloxone HCl dihydrate.[10-24] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In 1 of the included studies, intrathecal naloxone was used for pain management as an adjunct to intrathecal morphine; while naloxone is known as an opioid antagonist at doses between 10-40

mcg/kg, preclinical studies have shown analgesic effects with ultra-low doses (4 mcg/kg).[9] However, the authors noted that the benefit was predominantly evaluated in murine models or via the intravenous route in clinical investigations; results varied greatly, with some studies showing beneficial effect, while others had none.[9] The utility of naloxone in pain relief was suggested to be tied to decreased inflammation due to downregulation of proinflammatory cytokine expression and with increasing "the antinociceptive effect of morphine by blocking opioid receptor pathways."[9]

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[7,10,13,22]	4
Experimental[8,9,12,14-18,24]	9
Observational[11,19-21,23]	5

Table 4. Number of studies by country

Country	**Number of Studies**
Canada[15]	1
France[12,17]	2
Iran[8,9,16]	3
US[7,10,11,13,14,18-24]	12
	Total US: 12 Total Non-US Countries: 6

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Opioid reversal					
Ambalu *et al.*, 2016, US[10]	Case report	1 In-patient presenting for a repeat cesarean section and elective bilateral tubal ligation (0%, 31 y)	• Combined spinal-epidural with subarachnoid bupivacaine, fentanyl, and epinephrine (1) Intraoperative nausea and pruritus were treated with ondansetron, metoclopramide, diphenhydramine, and naloxone	Resolution of intraoperative nausea and pruritus	"This case demonstrates the successful use of combined spinal epidural analgesia for a C-section and bilateral tubal ligation in a patient with a history of chronic back pain, two lumbosacral laminectomies, and a spinal cord stimulator."
Beausang and Hsu, 2012, US[7]	Case	1 In-patient with delayed postoperative respiratory failure due to intrathecal opiate hypersensitivity (0%, 66 y)	• Spinal anesthesia with bupivacaine and morphine (1) Naloxone infusion was started when patients experienced respiratory depression	Resolution of respiratory failure and somnolence	The patient's improvement after naloxone administration and mask ventilation confirmed the diagnosis of opioid-induced respiratory depression

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Cozowicz *et al.*, 2019, US[11]	Retrospective population-based cohort analysis	265,538 In-patients receiving analgesia in lumbar spine fusion surgery Opioids only (45.1%, range 51-71 y) 1 mode (42.7%, range 51-70 y) 2 modes (40.7%, range 51-69 y) 2+ modes (40.6%, range 50-68 y)	• Opioids only (103,382) • 1 mode (103,382) • 2 modes (44,526) • 2+ modes (13,624) Total number of patients who received naloxone (4,133)	Inpatient opioid prescription dose	"While multimodal analgesia was not consistently implemented in spine fusion surgery, particularly NSAIDs and COX-2 inhibitors demonstrated opioid sparing effects. Moreover, results suggest a synergistic interaction between gabapentinoids and opioids, the former potentiating opioid effects resulting in greater naloxone requirement."
Gentili and Bonnet, 1996, France[12]	Double-blind, randomized	40 In-patients undergoing hip surgery during spinal anesthesia (gender not specified, range 41-77 y)	• Spinal bupivacaine with clonidine (20) • Spinal bupivacaine with morphine (20) Total number of patients who received naloxone (17)	Bladder distension, bladder catheterization, naloxone utilization	"We conclude that spinal clonidine impaired bladder function to a lesser extent than morphine."
Gerancher and Nagle, 2008, US[13]	Case report	1 In-patient post accidental spinal administration of extended-release epidural morphine (EREM; 0%, 45 y)	• Spinal extended-release epidural morphine (1) Naloxone infusion was given prophylactically in the postanesthesia care unit	Resolution of opioid side effects	"Rather, we believe this case does imply that preservation of an acceptable patient recovery is possible with appropriate and thoughtful management of known accidental spinal administration of EREM."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Gwirtz *et al.*, 1995, US[14]	Placebo-controlled, double-blinded prospective study	38 In-patients post major urologic surgery Placebo (81%, mean 45.3 y ± 3.8) Ketorolac (94%, mean 43.8 y ± 4.1)	• Placebo (21) • Ketorolac (17) Total number of patients who received naloxone (4)	Pain scores using visual analogue scale (VAS)	"When used in conjunction with subarachnoid opioids, the scheduled administration of intravenous ketorolac during the first 24 hours after major urologic surgery significantly enhances analgesia and reduces the need for supplemental intravenous opioids without affecting the incidence of side effects. Intravenous ketorolac is a safe and useful adjuvant to subarachnoid opioids in the management of acute postoperative pain."
Halpern *et al.*, 2004, Canada[15]	Multicenter, randomized controlled trial	242 In-patients receiving pain relief in labor Intravenous analgesia (0%, mean 27 y ± 5.8) Epidural analgesia (0%, mean 28 y ± 5.4)	• Intravenous analgesia (118) • Epidural analgesia (124) Total number of neonates who received naloxone (24)	Incidence of cesarean delivery in each treatment group	"PCEA [patient-controlled epidural analgesia] provides superior analgesia and less maternal and neonatal sedation compared with PCIA [patient-controlled intravenous analgesia]."
Hirmanpour *et al.*, 2015, Iran[16]	Randomized, prospective, double-blind study	88 In-patients receiving pruritus prophylaxis for spinal anesthesia in elective caesarean surgery Ondansetron (0%, mean 30.3 y ± 5.6) Propofol (0%, mean 28.9 y ± 4.8)	• Ondansetron (44) • Propofol (44) Total number of patients who received naloxone (10)	Incidence and severity of pruritus	Both interventions were safe and well-tolerated, and had similar efficacy; both can be used instead of naloxone for pruritus resulting from intrathecal sufentanil

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Hommeril *et al.*, 1994, France[17]	Double-blind, randomized study	32 In-patients post hip and knee arthroplasty (31%, range 42-83 y)	• Morphine (16) • Ketoprofen (16) Total number of patients who received naloxone (3)	Pain scores, pain reduction, additional analgesia requirement	"As there were few differences between i.v. ketoprofen and extradural morphine, we conclude that ketoprofen may be an efficient alternative to extradural morphine after hip and knee arthroplasty."
Jacobson *et al.*, 1988, US[18]	Double-blind study	33 In-patients receiving postoperative pain relief after total knee or hip replacement surgery (100%, range 51-74 y)	• Morphine 0 mg (10) • Morphine 0.3 mg (10) • Morphine 1 mg (10) • Morphine 2.5 mg (3) Total number of patients who received naloxone (3)	Modified rank pain scale, numerical pain rating system, supplementary analgesia requirements, adverse effects	"We conclude that no ideal dose of intrathecal morphine exists because, even with small quantities, minor adverse effects are evident. Doses between 0.3 and 1 mg, however, should provide good analgesia free from the major complication, respiratory depression."
Khelemsky *et al.*, 2015, US[19]	Retrospective cohort study	442,669 In-patients (40%, mean 60 y ± 16)	Total number of times naloxone was administered (433)	Receiving naloxone within 72 hours of operation	The overall incidence of postoperative naloxone administration in a 13-year period was 0.1%, with most cases occurring within the first 24 hours

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Metz *et al.*, 2004, US[20]	Retrospective noncontrolled chart review	150 In-patients undergoing off-pump coronary artery bypass grafting (gender and age not specified)	• Intrathecal morphine (112) • No intrathecal morphine (38) Total number of patients who received naloxone (5)	Intraoperative extubation rate, delayed respiratory depression, other complications potentially attributable to intrathecal morphine	"It is concluded that intrathecal morphine is associated with a high intraoperative extubation rate in patients undergoing off-pump coronary artery bypass grafting. The authors' practice included 24-hour respiratory monitoring to detect delayed respiratory depression."
Putnam *et al.*, 2015, US[21]	Retrospective review	128 In-patients receiving pain control after major urologic surgery Intrathecal morphine (26%, mean 7.24 y ± 3.40) Intravenous morphine (41%, mean 8.0 ± 2.97)	• Intrathecal morphine (77) • Intravenous morphine (51) Total number of patients who received naloxone (2)	Pain scores, need for rescue analgesics, opioid-related adverse events and their treatments	"We observed better postoperative pain control in children who received IT [intrathecal] vs IV [intravenous] opioids for the first 16 h with no discernible difference thereafter. The intrathecal group experienced higher incidences of pruritus, constipation, and hypotension."
Reed *et al.*, 2018, US[22]	Retrospective case study	13 In-patients who were transferred to the intensive care unit (ICU) for respiratory failure following spine surgery (62%, mean 60.8 y)	Total number of patients who received naloxone (3)	Characterization of common features of patients transferred to the ICU due to respiratory failure	"This study should draw attention to the importance of perioperative care in individuals with significant morbidity and higher levels of narcotic use."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Vanterpool *et al.*, 2010, US[23]	Retrospective cohort design	210 In-patients receiving postoperative pain control after total hip or knee arthroplasty Continuous epidural morphine (40.6%, mean 61.26 y ± 1.26) Single-dose epidural morphine (31.2%, mean 67.12 y ± 1.39)	• Continuous epidural morphine (101) • Single-dose epidural morphine (109) Total number of patients who received naloxone (6)	Analgesia, side effects, ambulation	"These results suggest that EREM [extended-release epidural morphine] is associated with better postoperative ambulation and analgesia during the transition to oral or intravenous analgesics, although a higher incidence of side-effects was evident."
Weddel and Ritter, 1980, US[24]	–	21 In-patients post elective abdominal, perineal, or lower extremity surgery with a continuous epidural block (gender and age not specified)	• Epidural morphine 5 mg/70 kg • Epidural morphine 10 mg/70 kg Total number of patients who received naloxone (1)	Serum morphine levels, analgesic effectiveness of epidural morphine	"This study demonstrated the analgesic effectiveness of epidural morphine and supports the concept of a direct spinal action…"
Indication 2: Pain management					
Firouzian *et al.*, 2020, Iran[9]	Randomized, double-blind, controlled clinical trial	77 In-patients undergoing lumbar laminectomy with spinal fusion Morphine with naloxone (gender not specified, mean 53.15 y ± 10.38) Morphine alone (gender not specified, mean 52 y ± 8.98)	• Intrathecal morphine with intrathecal naloxone (40) • Intrathecal morphine alone (37)	Pain severity with a standard VAS	Compared to morphine alone, the addition of intrathecal naloxone improved post-operative analgesia and reduced opioid-related side effects; further studies with larger sample sizes are needed

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Peivandi *et al.*, 2019, Iran[8]	Double-blind, randomized, clinical trial	70 In-patients who were scheduled for cesarean section under spinal anesthesia Study (0%, mean 31.34 y ± 6.14) Control (0%, mean 33.23 y ± 5.08)	• Spinal bupivacaine, morphine, and naloxone (35) • Spinal bupivacaine, morphine, and placebo (35)	Postoperative pain intensity	The authors concluded that the addition of intrathecal naloxone did not have a significant effect on postoperative pain intensity, but did, however, decrease severity of postoperative nausea and pruritus

Abbreviations: "–", not mentioned; COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug; VAS, visual analogue scale.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Opioid reversal[7,10,11,13,14,18-24]	40-13,000 mcg	–	–	–	16-22 hours
	40 mcg/hour				2 hours

Abbreviations: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Opioid reversal[12,15-17]	40-200 mcg	–	–	–	Once
	5 mcg/kg/hour				4 hours
Pain management[8,9]	20 mcg	–	–	Intrathecal	Once

Abbreviations: "–", not mentioned.

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Sixteen SMEs discussed naloxone HCl dihydrate. Amongst these 16 SMEs, there were 10 medical doctors, 5 pharmacists, and 1 dentist. The SMEs specialized and/or were board-certified in addiction medicine, addiction psychiatry, anesthesiology, critical care, oncology/hematology, oral and maxillofacial surgery, pain medicine, palliative care, pharmacotherapy, psychiatry, and primary care/family practice, working in academic medical centers, hospitals/health systems, and private practice/clinic. The SMEs had been in practice for 6 to 33 years.

Narcan® (naloxone) is an emergency class of drug; however, several SMEs that specialized in anesthesiology stated that if an anesthesiologist needs it during a medical procedure, they have not properly titrated the opioids to the patient's respiratory rate, something that occurs with inexperienced resident physicians. If the patient is exhibiting respiratory depression, the SME commented that since they are managing the patient's airway, they can ventilate the patient and focus on opioid reversal later. Standard anesthesiology practice is not to reverse opioids with naloxone, but to wait. The SME stated that it would be needed more "on the floor" since opioids are not titrated there, and you do not have a safe airway. Naloxone was described as being compounded frequently, with ampoules of 0.4 mg/mL diluted 1:10 to reverse narcotics if the patient is slow to emerge from anesthesia or is not breathing; it is not advised to give the full dose of naloxone all at once. Instead, the anesthesiologist administers a small dose of naloxone and waits a few minutes to see if the patient has spontaneous breathing before giving the next dose. Since it is used infrequently by anesthesiologists, the SME did not think it would be helpful to have the diluted form pre-prepared.

Outside the hospital, one SME reported using naloxone in their dental practice, where they keep it in their crash cart just in-case they put the patient to sleep and need to use it. One SME who works in pain management reported giving all patients a prescription for intranasal naloxone to circumvent opioid overdose, though it requires the patient to have someone else around to administer it to them. When asked if they thought there was utility in higher concentrations of naloxone, another SME responded that "it should come in basic smaller doses which you can use."

When asked about the different ROA, one SME said that they typically only use naloxone intravenously; however, they could see administering intramuscularly or by intraosseous route if unable to obtain an intravenous line, though they had not done it themself. They had not administered naloxone via the intrathecal route and could not see a reason to do so. One SME said that they have never seen Narcan®

(naloxone) used intrathecally in 20 years of practice. However, another SME said that they had administered intrathecal naloxone to reverse an opioid overdose for a patient with a pain pump in the spinal cavity. However, this was the only time they had done this in 6 years; they only administered via this route because they already had access, but they try to avoid this if possible. Some SMEs mentioned having heard of naloxone via intrathecal/epidural route as pain management/anesthesia, but not as an addiction medication. In this scenario, it was used with intrathecal morphine. Otherwise, in the hospital it is predominately intramuscular or intravenous administration, with the occasional intranasal administration in the emergency department. One SME said that in the 1990s, some anesthesiologists would administer intrathecal morphine or hydromorphone alongside low-level intravenous naloxone infusion, but this is less common now.

Other routes mentioned by SMEs include subcutaneous and sublingual in combination with buprenorphine and oxycodone. The intent behind using naloxone in combination is to "take the edge off some of the addiction potential of the opioid stuff." The SME also prescribed naloxone to patients who are placed on narcotics and educate the people who live with the patient on how to utilize it in the scenario of an opioid overdose.

One SME said that they thought naloxone would be useful as a patch, "because patients who are strung out, sometimes it is useful to slap a patch on and you are done. All these things are good in patches."

Another SME said they did not use naloxone.

Results of survey

A separate survey was distributed by the Ambulatory Surgery Center Association (ASCA); 230 people responded to this survey (refer to Appendix 2.2 for survey instrument). Zero people responded to the survey distributed via professional medical associations and available on the project website.

Amongst respondents to the ASCA survey, 97 (42% of 230 total respondents) were very familiar with the term '503B outsourcing facility', 86 (37%) were somewhat familiar with this term, and 47 (20%) were not familiar with this term (refer to Table 15).

One hundred ten survey respondents (54% of 203 people who responded to this question) utilized a 503B outsourcing facility to acquire compounded drugs; 93 survey respondents (46%) did not utilize a 503B outsourcing facility. Five respondents (1.8% of 290 responses, where respondents were allowed to select multiple drug products) obtained naloxone from a 503B outsourcing facility (refer to Table 16).

The most common types of procedures performed at the facilities where the ASCA survey respondents worked were: ophthalmology (115, 17% of responses, where respondents were allowed to select multiple procedure types); orthopedics (89, 13%); pain (80, 12%); podiatry (74, 11%); and plastics (72, 10%) (refer to Table 17).

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which naloxone HCl dihydrate prescribed or administered

No respondents to survey distributed to professional medical associations

Table 13. Reasons for using compounded naloxone HCl dihydrate

No respondents to survey distributed to professional medical associations

Table 14. Use of non-patient-specific compounded naloxone HCl dihydrate

No respondents to survey distributed to professional medical associations

Table 15. Ambulatory Surgery Center Association respondents' familiarity with compounding terms

Compounded drugs (medications prepared to meet a patient-specific need)	**Responses, n (N=230)**
Very familiar	153
Somewhat familiar	70
Not familiar	7
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed to meet a patient-specific need)	**Responses, n (N=230)**
Very familiar	118
Somewhat familiar	91
Not familiar	21
503B Outsourcing facility (a facility that compounds larger quantities without a patient-specific prescription)	**Responses, n (N=230)**
Very familiar	97
Somewhat familiar	86
Not familiar	47

Table 16. Products obtained from a 503B outsourcing facility

Product	**Responses, n (N=290)[a]**
Amitriptyline / Ketoprofen / Oxymetazoline	1
Budesonide	2
Calcium gluconate	2
Droperidol	2

Epinephrine	11
Epinephrine for ophthalmic administration	16
Epinephrine / Lidocaine for ophthalmic administration	31
Epinephrine / Bupivacaine / Fentanyl	3
Fentanyl	10
Flurbiprofen	3
Flurbiprofen for ophthalmic administration	6
Hydromorphone	5
Ipamorelin	1
Ketoprofen / Nifedipine	3
Lidocaine / Epinephrine / Tetracaine	13
Meperidine	3
Morphine	5
Naloxone	5
Neomycin	5
Phentolamine	1
Promethazine	5
Remifentanil	4
Sufentanil	2
Tramadol	2
None of the above	75
Do not obtain any compounded drugs from 503B outsourcing facility	74

[a]Survey respondents allowed to select multiple products.

Table 17. Type of specialty procedures performed at ambulatory surgery facility

Procedure Type	Responses, n (N=230)[a]
Dental	23
Dermatology	9
Endoscopy	65
Neurosurgery	22
Obstetrics/gynecology	39
Ophthalmology	115
Otolaryngology	58
Orthopedics	89
Pain	80
Plastics	72
Podiatry	74
Other[b]	40

[a]Survey respondents allowed to select multiple procedure types.
[b]No respondents provided description for 'Other' procedure type.

CONCLUSION

Naloxone HCl dihydrate was nominated for inclusion on the 503B Bulks List for opioid overdose via injection through intrathecal, intramuscular, subcutaneous, and intravenous routes. Naloxone HCl dihydrate is approved 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 and interviews, indications for naloxone HCl dihydrate included opioid reversal and pain management. When a patient is undergoing procedures in the hospital, typically their airway is managed closely by an anesthesiologist, and standard practice is not to use naloxone, but to wait and ventilate the patient if necessary. When naloxone is used in a hospital setting, it is diluted and administered in small doses, waiting a few minutes to check for spontaneous breathing before providing the next dose. In the hospital, naloxone is typically administered via intravenous or intramuscular injection, with intranasal administration in the emergency department. There was only one situation where an SME reported having administered naloxone via the intrathecal route, and that was for a patient who had a spinal pump, and therefore intrathecal access was already established. As an opioid antagonist, naloxone's capacity for being used in opioid overdose is well-known, but pain management was less familiar. Preclinical studies have found analgesic effects with naloxone at ultra-low doses; however, these benefits were shown in either murine models or via intravenous administration. The mechanism was suggested to be connected to decreased inflammation and increasing analgesia through blocking opioid receptor pathways. None of the SMEs reported having used naloxone in this manner, though one had heard of the possibility.

From the responses to the ASCA survey, 5 respondents (1.8% of 290 responses, where respondents were allowed to select multiple drug products) obtained naloxone from a 503B outsourcing facility.

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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 March 26, 2020
- Date last searched: March 30, 2020
- Limits: Humans (search hedge); English language
- Number of results: 468

1	naloxone/	18642
2	nalosson$.tw.	0
3	nalaxon$.tw.	13
4	naloxon$.tw.	23366
5	or/1-4	27155
6	infusions, spinal/	152
7	exp injections, spinal/	15966
8	epidural space/	4478
9	spinal$.tw.	263555
10	intraspinal$.tw.	4983
11	epidural$.tw.	41558
12	extradural$.tw.	6695
13	extra dural$.tw.	139
14	peridural$.tw.	2057
15	peri dural$.tw.	6
16	caudal$.tw.	45086
17	intracaudal$.tw.	11
18	arachnoid$.tw.	8047
19	subarachnoid$.tw.	35067
20	intrathecal$.tw.	23455

21	intra thecal$.tw.	74
22	neuraxial$.tw.	2535
23	or/6-22	385839
24	exp opioid-related disorders/	25903
25	drug overdose/	11149
26	exp analgesia/	43540
27	exp pain/	390010
28	pain management/	32996
29	analgesics, opioid/	43150
30	dt.fs.	2190148
31	ad.fs.	1396708
32	tu.fs.	2196097
33	pc.fs.	1267246
34	overdos$.tw.	22324
35	intoxic$.tw.	45933
36	toxic$.tw.	616620
37	analges$.tw.	120954
38	pain$.tw.	676639
39	opioid$.tw.	87334
40	opiate$.tw.	24581
41	narcotic$.tw.	15125
42	or/24-41	5603893
43	and/5,23,42	2647
44	exp animals/ not humans/	4683273
45	43 not 44	532
46	limit 45 to english language	468

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 March 26, 2020
- Date last searched: March 30, 2020
- Limits: Humans (search hedge); English language
- Number of results: 32

1	naloxone/	18642
2	nalosson$.tw.	0
3	nalaxon$.tw.	13
4	naloxon$.tw.	23366
5	or/1-4	27155
6	exp migraine disorders/	26852
7	migrain$.tw.	34417
8	or/6-7	38797
9	and/5,8	43
10	exp animals/ not humans/	4683273
11	9 not 10	38
12	limit 11 to english language	32

Embase search strategy 1

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 30, 2020
- Limits: Humans (search hedge); English language
- Number of results: 677

1	naloxone'/mj	21048
2	nalosson*':ti,ab,tn	0
3	nalaxon*':ti,ab,tn	37
4	naloxon*':ti,ab,tn	28208
5	#1 OR #2 OR #3 OR #4	35319
6	intraspinal drug administration'/de	3444
7	epidural drug administration'/de	8848
8	intrathecal drug administration'/de	20957
9	intracaudal drug administration'/de	16
10	epidural space'/de	6318
11	spinal*':ti,ab	362058
12	intraspinal*':ti,ab	6716
13	epidural*':ti,ab	58667
14	extradural*':ti,ab	8873
15	extra dural*':ti,ab	238
16	peridural*':ti,ab	2986
17	peri dural*':ti,ab	12
18	caudal*':ti,ab	58164
19	intracaudal*':ti,ab	17
20	arachnoid*':ti,ab	12159
21	subarachnoid*':ti,ab	49589
22	intrathecal*':ti,ab	34652

23	intra thecal*':ti,ab	230
24	neuraxial*':ti,ab	4259
25	#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	534641
26	opiate addiction'/de	19880
27	drug overdose'/de	27555
28	drug intoxication'/de	22155
29	analgesia'/exp	169703
30	pain'/exp	1364541
31	narcotic analgesic agent'/exp	344944
32	drug dose':lnk	622308
33	drug administration':lnk	1723135
34	drug therapy':lnk	3853707
35	prevention':lnk	1161765
36	overdos*':ti,ab	34112
37	intoxic*':ti,ab	69721
38	toxic*':ti,ab	884427
39	analges*':ti,ab	178272
40	pain*':ti,ab	1037947
41	opioid*':ti,ab	118695
42	opiate*':ti,ab	34017
43	narcotic*':ti,ab	23580
44	#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 OR #43	7137647
45	#5 AND #25 AND #44	3435
46	[animals]/lim NOT [humans]/lim	6010640
47	#45 NOT #46	813
48	#45 NOT #46 AND [english]/lim	677

Embase search strategy 2

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 30, 2020
- Limits: Humans (search hedge); English language
- Number of results: 47

1	naloxone'/mj	21048
2	nalosson*':ti,ab,tn	0
3	nalaxon*':ti,ab,tn	37
4	naloxon*':ti,ab,tn	28208
5	#1 OR #2 OR #3 OR #4	35319
6	migraine'/exp	66228
7	migrain*':ti,ab	55110
8	#6 OR #7	72431
9	#5 AND #8	76
10	[animals]/lim NOT [humans]/lim	6010640
11	#9 NOT #10	61
12	#9 NOT #10 AND [english]/lim	47

Appendix 2.1 Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded naloxone HCl dihydrate. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly,
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

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)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer naloxone HCl dihydrate to your patients?

    - o Yes
    - o No

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

    - o Intrathecal injection
    - o None of the above

4. I prescribe or administer naloxone HCl dihydrate for the following conditions or diseases: (check all that apply)

    - o Opioid overdose
    - o Therapeutic reversal of opioids
    - o Other (please explain) _____

5. I use naloxone HCl dihydrate with my patients as the following (check all that apply)

    - o FDA-approved product
    - o Compounded drug product
    - o Other (please explain) _____

6. I use compounded naloxone HCl dihydrate because: (check all that apply)

    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain)_____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing naloxone HCl dihydrate.
    - o Other (please explain) _____

7. Do you stock non-patient-specific compounded naloxone HCl dihydrate at your practice?

    - o Yes
    - o No
    - o I'm not sure

8. I obtain compounded naloxone HCl dihydrate from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

9. What is your practice setting? (check all that apply)

    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please describe) _____

10. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 2.2 Survey instrument for Ambulatory Surgery Center Association

Welcome. We want to understand your clinical use of compounded drugs. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in bulk compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

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)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you utilize a 503B outsourcing facility to acquire compounded drugs?

   - o Yes. If yes, why? _____
   - o No. If no, why not? _____

3. Do you obtain any of the following products from a 503B outsourcing facility? (check all that apply)

   - o I do not obtain any compounded drugs from 503B outsourcing facilities
   - o Amitriptyline / Ketoprofen / Oxymetazoline
   - o Budesonide
   - o Calcium gluconate
   - o Droperidol
   - o Epinephrine
   - o Epinephrine for ophthalmic administration
   - o Epinephrine / Lidocaine for ophthalmic administration
   - o Epinephrine / Bupivacaine / Fentanyl
   - o Fentanyl
   - o Flurbiprofen
   - o Flurbiprofen for ophthalmic administration
   - o Hydromorphone
   - o Ipamorelin
   - o Ketoprofen / Nifedipine
   - o Lidocaine / Epinephrine / Tetracaine HCl
   - o Meperidine
   - o Morphine
   - o Naloxone
   - o Neomycin
   - o Phentolamine
   - o Promethazine
   - o Remifentanil
   - o Sufentanil

- o Tramadol
- o None of the above

4. What type of specialty procedures are performed in your facility? (check all that apply)

- o Dental
- o Dermatology
- o Endoscopy
- o Neurosurgery
- o Obstetrics/gynecology
- o Ophthalmology
- o Otolaryngology
- o Orthopedics
- o Pain
- o Plastics
- o Podiatry
- o Other (please describe) _____

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations that declined in Year 1 were not contacted in Year 2.