Summary Report

Morphine sulfate

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

API	Active Pharmaceutical Ingredient
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 Food and Drug Administration (FDA) in their evaluation of the use of morphine sulfate/morphine sulfate pentahydrate (UNII code: X3P646A2J0), 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 morphine sulfate is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how morphine sulfate 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 morphine sulfate and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Morphine sulfate was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA), Pentec Health, the Sterile Specialty Pharmaceutical Society (SSPS), and US Compounding Pharmacy.

Morphine sulfate was nominated as an oral liquid and various injectable products (intrathecal, epidural, intramuscular, subcutaneous, and intravenous) in strengths 0.05-100 mg/mL for:

- Diabetic neuropathy
- Diarrhea
- Dyspnea
- Procedural sedation
- Rapid-sequence intubation
- Acute, chronic, and severe pain (such as chronic non-malignant and cancer pain)

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

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

- Compounded product may be the only product to effectively treat the indication for which it is intended
- Patient need for dosage form or strength, including greater concentration, that is not available commercially
- Patient sensitivities to dyes, fillers, preservatives or other excipients in manufactured products
- Manufacturer backorder
- 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
- According to SPSS, 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 morphine sulfate products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in 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 morphine sulfate; name variations of morphine sulfate were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing morphine sulfate. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

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

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances morphine sulfate was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify the following medical specialties that would potentially use morphine sulfate: anesthesiology, pain management, 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 morphine sulfate in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project 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

- Morphine sulfate is available as an FDA-approved product in the nominated dosage form and ROA.
- Morphine sulfate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for morphine sulfate.
- Morphine sulfate is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, and UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Morphine sulfate	0.5-25 mg/mL	Solution	Injection, intramuscular, intravenous, subcutaneous	Prescription	09/18/1984
	10-200 mg	Extended release capsule, tablet, extended release tablet	Oral		05/29/1987
	2-20 mg/mL	Solution			03/17/2008

[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]
Morphine sulfate	0.5-60 mg/mL	Solution, suspension	Epidural, injection, intramuscular, intravenous, subcutaneous	Abu Dhabi	Active	–
				Australia	(S8) Controlled drug	08/13/1991
				Canada	Narcotic (CDSA 1)	12/31/1978
				Hong Kong	Prescription only medicine	02/04/1987
				Ireland	Prescription-only non-renewable	04/01/1978
				New Zealand	Class B1 Controlled Drug	04/28/1983
				Saudi Arabia	Prescription	–
				UK	Prescription-only medication	01/19/1982
	5-200 mg 1-20 mg/mL	Extended release tablet, sustained release capsule, tablet, suspension, granules, solution, syrup	Oral	Abu Dhabi	Active	–
				Australia	(S8) Controlled drug	04/20/2005
				Belgium	Medical prescription	04/29/1986
				Canada	Narcotic (CDSA 1)	12/31/1985
				Hong Kong	Prescription only medicine	08/23/1999
				Ireland	Prescription-only non-renewable	04/19/1982
				Namibia	–	02/07/1984
				New Zealand	Class B1 Controlled Drug	06/28/1984

				UK	Prescription-only medication	03/08/1988

Abbreviation: "– ", 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.

Results of literature review

No literature review was conducted.

Pharmacology and historical use

Four studies were identified that provided valuable information about the pharmacology and historical use of morphine sulfate.

In epidural administration, lipophilic drugs demonstrate fewer side effects and reduced risk of delayed respiratory depression, but the analgesic action is limited to segmental distribution and requires catheter placement at or near the level of surgery.[8] On the other hand, hydrophilic opioids have better analgesia that is not segmentally limited, but are associated with increased delayed respiratory depression, as well as other opioid-related side effects.[8] Hydrophilic opioids, like morphine and hydromorphone, are commonly used in continuous epidural infusions, and "may provide more reliable neuraxial analgesia than the more lipophilic opioids such as fentanyl and sufentanil."[9]

Intrathecal opioid administration offers benefits over epidural administration in a faster onset and lower systemic spread.[10] As with epidural administration, the lipophilicity of the chosen opioid is an important consideration; more lipophilic drugs, such as fentanyl and sufentanil, are removed from the cerebrospinal fluid very quickly, which results in them having an effect on fewer spinal levels.[10] More hydrophilic drugs, such as morphine and hydromorphone, have demonstrated a greater rostral spread and a significant effect across multiple spine levels in comparison.[10] Like with epidural administration, more hydrophilic opioids are associated with a delayed, but longer duration of analgesia, as well as an increased incidence of side effects while more lipophilic agents have a faster onset of analgesia, but a shorter duration of action and decreased side effects.[11]

The FDA has recommended that intrathecal drug therapy is indicated for moderate-to-severe trunk and limb pain, and intractable pain that has been refractory to conservative treatment attempts; the Polyanalgesic Consensus Conference (PACC) noted that while there is interest in using intrathecal therapy to cover focal extremity pain, support in the literature is lacking, with only anecdotal reports.[12] More specific disease indications for intrathecal drug delivery included: axial neck or back pain in patients who were not candidates for surgery (multiple compression fractures, discogenic pain, spinal stenosis, diffuse multiple-level spondylosis); failed back surgery syndrome; abdominal or pelvic pain (visceral, somatic); extremity pain (radicular pain, joint pain); complex regional pain syndrome; trunk pain (postherpetic neuralgia, post-thoracotomy syndromes); cancer pain (direct invasion and chemotherapy-related); and situations where analgesic efficacy with systemic opioid delivery is complicated by intolerable side effects.[12]

In 2019, an article reviewed morphine and ziconotide as first-line options for intrathecal therapy in patients with chronic pain.[13] The authors were members of the PACC, an organization that "was formed in 2000 to review evidence pertaining to the efficacy and safety of [intrathecal] therapies and provide published guidelines regarding their use."[13] The authors noted that morphine and ziconotide are the only agents that are FDA-approved as intrathecal therapies for chronic pain.[13] When reviewing the literature, the majority of studies demonstrating the efficacy of intrathecal morphine for both cancer-related and non-cancer-related pain were noncontrolled, prospective, and retrospective studies.[13]

Table 3. Types of studies

No literature review was conducted

Table 4. Number of studies by country

No literature review was conducted

Table 5. Summary of included studies

No literature review was conducted

Table 6. Dosage by indication – US

No literature review was conducted

Table 7. Dosage by indication – non-US countries

No literature review was conducted

Table 8. Number of studies by combination

No literature review was conducted

Table 9. Compounded products – US

No literature review was conducted

Table 10. Compounded products – non-US countries

No literature review was conducted

Results of interviews

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. Twenty SMEs discussed morphine sulfate. Amongst these 20 SMEs, there were 10 medical doctors, 5 pharmacists, 1 nurse practitioner, 1 physician assistant, and 3 dentists. The SMEs specialized and/or were board-certified in anesthesiology, compounding, dentistry, emergency medicine and critical care, oncology and hematology, oral and maxillofacial surgery, orthopedics, pain medicine, palliative care, pharmacotherapy/pharmacology, pediatric anesthesia, psychiatry, and primary care and family practice, working in academia, academic medical center, hospital/health system, pharmacy/pharmaceutical company, and private practice/clinic. The SMEs had been in practice for 6 to 39 years.

The main limiting factors with morphine sulfate use are the side effects: nausea and pruritus associated with histamine release. The pruritus can range from mild to "scratch your skin off" and is especially common with intrathecal or epidural morphine sulfate administration. As a result, one anesthesiologist SME said that they do not see the benefit of using morphine sulfate via these routes; they speculated that it may be related to cost but stated that the science should be the major consideration. Another anesthesiologist said that they treat side effects with Claritin® (loratadine), Benadryl® (diphenhydramine), and Nubain® (nalbuphine, a mixed opioid agonist/antagonist). They recalled using Narcan® (naloxone) in one situation where the other therapies were not working and Nubain® was unavailable. One SME said that they never use morphine sulfate; they prefer fentanyl or hydromorphone because these drugs have a "cleaner profile" regarding histamine release and mutagenicity.

One anesthesiologist said that most elective cesarean sections are done under spinal anesthesia with bupivacaine, fentanyl, or Duramorph® (morphine sulfate). Epidurals are only used for elective cesarean sections if a catheter is already in place from labor and before they remove the epidural catheter, they will add Duramorph® (morphine sulfate) so the patient can recover and be able to walk. Another anesthesiologist said that they do not use epidural anesthesia as much in pediatric patients because accessing the epidural space is more challenging, and the patient must be asleep, so practitioners lose the ability to receive feedback. However, they will use morphine sulfate in small children because of the predictable metabolism and do administer it via the epidural route in pediatric patients. Several anesthesiologists mentioned that there is a fair amount of waste with intrathecal and epidural administration; they only use a small amount and end up throwing the rest away. Otherwise, morphine sulfate is typically administered intravenously.

When asked about rapid-sequence intubation (RSI), one anesthesiologist said that narcotics can be used to blunt airway reflex. It is very stimulating for a laryngoscope to be put in and for the patient to be intubated and narcotics will blunt the hemodynamic response and prevent tachycardia and hypertension. Once the patient is intubated, it is still stimulating for them, so they want to blunt the airway reflex. Several anesthesiologist SMEs said that they would use fentanyl before they would use morphine sulfate; fentanyl is lipophilic and has a faster onset of action whereas morphine sulfate is more hydrophilic and sticks around the body longer. Additionally, fentanyl was described as better at blunting the reflex response and more sedating when compared to morphine sulfate.

A couple of anesthesiologist SMEs said that there is a movement to use less narcotics in patients, or to only use non-synthetic opioids. They said that they typically use Tylenol® (acetaminophen) preoperatively and ketamine and Precedex® (dexmedetomidine) intraoperatively. When they do use opioids, most of the anesthesiologist SMEs used fentanyl, morphine sulfate, or hydromorphone in their practice. One anesthesiologist said that opioids such as Dilaudid® (hydromorphone) are utilized in the post anesthesia care unit (PACU) where ketamine and dexmedetomidine are unavailable. Several

anesthesiologists said that intravenous morphine is administered if the patient has an allergy to Dilaudid® (hydromorphone). One SME said that morphine sulfate is superior to Dilaudid®, but when Dilaudid® came off-patent, it ended up being used more often and intravenous morphine sulfate became second line. The PACU also administers intravenous morphine sulfate for angina. One anesthesiologist said that oral morphine sulfate has an advantage over other opioids in treatment of chronic pain due to a time-release matrix.

The SMEs who specialized in dentistry said that they use nonsteroidal anti-inflammatory drugs (NSAIDs) and oral opioids for postoperative pain management. Typically, they use a combination that includes Tylenol®, such as Tylenol #2 or Tylenol #3 (acetaminophen and codeine), Norco® (acetaminophen and hydrocodone), or Percocet® (acetaminophen and oxycodone). They may also use NSAIDs such as etodolac or ibuprofen. One SME said that they occasionally use tramadol if a patient is unable to take another opioid due to allergy; sometimes they also use morphine. Other SMEs said that they do not use morphine sulfate at all. One SME said that there are more hoops to jump through with using opioids of high abuse potential such as fentanyl or morphine sulfate, so they do not keep them on hand.

One SME who specialized in oncology said that while oxycodone and morphine sulfate are similar drugs, they usually start with oxycodone unless dictated by the insurance. Both SMEs said that they prescribe pain medications based off what their formulary will cover. They try to keep the same active product for the patient's short-acting break-through therapy and long-acting maintenance therapy. For example, if they used short-acting morphine sulfate, they would want the extended release morphine sulfate instead of having the patient on a combination of morphine sulfate and oxycodone. They use fentanyl patches frequently, especially with patients who have head and neck cancer and cannot take things by mouth. They also said that they are using more methadone.

An SME who specialized in orthopedics said that they use a compounded combination injection with morphine, bupivacaine, and epinephrine for pain control in patients receiving total knee replacement. It is now part of the order set for the procedure and is made in the hospital pharmacy. Because of soft tissue trauma associated with the total knee procedure, the combination is injected around the incision site.

One SME who specialized in pain management said that they do not do a lot of intrathecal pump administration anymore; they tend to see patients who have an intrathecal pump who want to switch to oral administration. As a result, they do not put patients on a pump unless they are committed to being on the pump without high doses of opioids. Typically, these are cancer patients, but they have non-cancer patients on the pumps as well. They use Prialt® (ziconotide). There are other drugs that they use via intrathecal administration, but the only ones that are FDA-approved are baclofen, morphine, and Prialt®. One SME said that they thought people would need the compounded product because it is cheaper. They get their intrathecal morphine sulfate compounded, but for the other ROA (intravenous, intramuscular, or subcutaneous) they get it from the manufacturer. One SME who specialized in psychiatry said that they had heard of intrathecal morphine sulfate being used with naloxone for pain management.

The palliative care SMEs said that morphine sulfate is commonly used in their practice. Their "work-horse drugs" are generic long-acting morphine, oral morphine solution, and oral methadone tablets and solution. They also use a good amount of hydromorphone and a lot of prescribers like oxycodone or hydrocodone either alone or with acetaminophen for breakthrough pain. One SME said that they wish they had the injectable morphine available in a higher concentration because while morphine is generally the least expensive intravenous opioid, they cannot get it into a small enough volume to use it. Morphine sulfate is also available as a rectal suppository and for intrathecal administration at a patient-specific concentration. One SME said that they try not to use neuraxial administration (such as intrathecal or epidural routes) if they can help it. They do inherit hospital patients who have implanted pumps; this is a

problem because the patient is likely going to die in 3 weeks, the implanted pump will run dry in one week, it costs $1000 to refill the pump, and the practitioners do not think the pump is really working in the first place.

One SME who works in primary care said that the oral opioids they prescribe most often are oxycodone, hydrocodone, methadone, and morphine sulfate. In their practice they typically use a combination of long and short-acting pain medications. The SME added that they consider morphine sulfate the gold standard and could see a need for a compounded morphine sulfate product in order to allow it to be combined with antiemetics, making it more tolerable to the patients. Another SME said that all opioids should come in a patch format, which would be helpful for the outpatient population.

One pharmacist SME said that they batch their own morphine patient-controlled analgesia (PCA) and keep 4-5 on hand. Another SME stated that their hospital system has not been able to get PCA from outsourcing facilities in the past few years due to opioid shortages. They need products in different concentrations than are commercially available for pediatric patients; they use PCAs for pain relief, their high volume pediatric intensive care unit (PICU), and oncology patients. Additionally, sometimes they need high concentrations of opioids due to some patients having volume restrictions. There are advantages to purchasing the opioids in ready-to-use syringes to keep on-hand in the nursing unit due to quick access and extended beyond use date (BUD). They would like to get hydromorphone HCl, along with morphine and fentanyl, from outsourcing facilities.

As far as compounded anesthetics are concerned, one SME who specialized in anesthesiology said that they used single ingredient drugs in anesthesia; they had no experience with compounding multiple powders together. Furthermore, they rarely mix products in the same syringe stating that this is frowned upon due to potential compatibility concerns. The exception would be regional or epidural anesthesia where they might add fentanyl or morphine to a local anesthetic to reduce the number of injections. Several SMEs who specialized in anesthesiology talked about using prefilled syringes that were produced by a third party and added that the Anesthesia Patient Safety Foundation (APSF) and the Joint Commission prefer that anesthesiologists use prefilled syringes; drawing up each product increases the potential for error and sterility concerns and that prefilled syringes offer less waste and fewer errors, though it is also more expensive. One SME said that epidural infusions are typically compounded by the hospital pharmacy, though perioperative antibiotics are either prepared by the pharmacy or the anesthesiologist themselves in the operating room. Another SME said that they see compounded drugs as convenient, but the only real application would be for epidural mixes. Everything else is typically mixed by the anesthesiologists themselves before administration. An SME said that their outsourcing facility finds epidurals an "inconsistent practice;" they use different concentrations of fentanyl and sometimes use morphine sulfate, with either ropivacaine or mepivacaine as the anesthetic. The outsourcing facility can "drive standardization," taking care of the epidurals that practitioners use for 80-90% of patients and leaving the custom mixtures for the hospitals to make themselves. One of the anesthesiologists said that they have had problems with drugs being on shortage. In some cases, they can adjust, for example if fentanyl is on backorder, then they can use morphine and alter their technique. Other drugs, such as backordered propofol, do not have alternatives. They noted that outsourcing facilities typically have a 2-3-month lead-in time between when the drug goes on shortage and when they are able to produce the product.

Several anesthesiologist SMEs said that they could not think of a situation where they would want to use a higher concentration opioid than what is already commercially available. One SME who specialized in dentistry said that compounded drugs for dentistry typically are topical local anesthetics. One SME who specialized in palliative care said that they try to minimize the use of compounded drugs due to limited

data. Furthermore, they said that "A lot of hospice nurses suffer under a misperception about compounds. Hospice nurses tend to think you can take any tablet or capsule and put it into the rectum and everything is great, which is not true. They think anything you put into a base, you can slab it onto intact skin and it's going to be absorbed and do well. It is not true. I am not a fan."

Results of survey

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

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).

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 (1.7% of 290 responses, where respondents were allowed to select multiple drug products) obtained morphine sulfate from a 503B outsourcing facility (refer to Table 15).

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 16).

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which morphine sulfate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded morphine sulfate

No respondents to survey distributed via professional medical associations

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

No respondents to survey distributed via 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=686)[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 were allowed to select multiple procedure types.
[b]No respondents provided description for 'Other' procedure type.

CONCLUSION

Morphine sulfate was nominated for inclusion on the 503B Bulks List as an oral liquid and various injectable products (intrathecal, epidural, intramuscular, subcutaneous, and intravenous) to treat diabetic neuropathy, diarrhea, dyspnea, and acute, chronic and severe pain (such as chronic non-malignant and cancer pain). It was also nominated in use for procedural sedation and rapid-sequence intubation. Morphine sulfate is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, and the UK.

From the literature review and interviews, morphine sulfate is commonly used in continuous epidural infusions. Due to the more hydrophilic nature of the drug, morphine sulfate provides better analgesia compared to the more lipophilic opioids but is associated with increased respiratory depression and other side effects. Intrathecal administration of opioids generally is associated with faster onset and lower systemic spread. Lipophilic drugs are removed from the cerebrospinal fluid quicker, producing a more local effect. Hydrophilic agents such as morphine sulfate has a greater spread across multiple spinal levels. Similarly, to epidural administration, hydrophilic drugs are associated with a delayed, but longer duration of analgesia, as well as increased incidence of side effects. Morphine is one of two drug products that are FDA-approved as intrathecal therapies for chronic pain, the second being ziconotide.

According to SMEs who specialized in anesthesiology, the main limiting factor with the use of morphine sulfate are the side effects, namely nausea and pruritus associated with histamine release. The pruritus is especially common with epidural or intrathecal administration and can range from mild to “scratch your skin off.” Drug classes that are used to treat the side effects are antihistamines and opioid antagonists or mixed agonists/antagonists. Some practitioners prefer to avoid use of morphine sulfate due to these side effects while others prefer it due to reliable pharmacokinetics and long history of use. Morphine sulfate is used in all the routes of administration nominated for use. While it was nominated for rapid-sequence intubation, anesthesiologists agreed that they would prefer fentanyl for this indication due to a faster onset of action and improved sedation when compared to morphine sulfate.

Zero people responded to the survey distributed via professional medical associations and available on the project website. Amongst respondents to the ASCA survey, 5 respondents (1.7% of 290 responses, where respondents were allowed to select multiple drug products) obtained morphine sulfate from a 503B outsourcing facility.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

No literature review was conducted.

Appendix 2.1. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded morphine sulfate. 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 morphine sulfate to your patients?
   - o Yes
   - o No

3. I prescribe or administer morphine sulfate for the following conditions or diseases: (check all that apply)
   - o Diabetic neuropathy
   - o Diarrhea
   - o Dyspnea
   - o Moderate-to-severe pain
   - o Procedural sedation
   - o Rapid-sequence intubation
   - o Other (please explain) _____

4. I used morphine sulfate with my patients as the following: (check all that apply)
   - o FDA-approved drug
   - o Compounded drug product
   - o Other (please describe) _____

5. I use compounded morphine sulfate 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 morphine sulfate.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded morphine sulfate at your practice?
    - o Yes
    - o No
    - o I'm not sure

7. I obtain compounded morphine sulfate 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) _____

8. 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) _____

9. 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.