Summary Report

Droperidol

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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
IM	Intramuscular
IRB	Institutional Review Board
IV	Intravenous
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 droperidol (UNII code: O9U0F09D5X), 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 droperidol 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 droperidol 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 droperidol 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

Droperidol was nominated for inclusion on the 503B Bulks List by Pentec Health, Specialty Sterile Pharmaceutical Society (SSPS), and US Compounding Pharmacy. Droperidol was nominated for treating, among other things, severe pain such as chronic non-malignant pain, and prophylaxis for nausea and vomiting via an intravenous (IV), intramuscular (IM), and/or intrathecal injection solution up to 2.5 mg/mL.

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

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

- Practitioners often prescribe doses that require higher strengths or concentrations than those available in FDA-approved products or use in combinations with other medications.
- If the FDA-approved, single-use only vials were used for compounding and the vial was punctured a second time or the vial's contents were used for more than one patient, then the compounding pharmacy would be using the product off-label.
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical size batch for outsourcing facilities; a single vessel compounded from bulk active pharmaceutical ingredient (API) is safer and more efficient than unmanageable amounts of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100 percent potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- According to SSPS, in order to utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.
- Manufacturer backorder.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of droperidol 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 droperidol; name variations of droperidol 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 droperidol. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe two concepts: droperidol and intrathecal administration (refer to Appendix 1 for full search strategies). The other nominated ROAs were not included in the literature review because there is an FDA-approved injectable droperidol product for IV or IM use. 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 12, 2020. In addition, the ECRI Guidelines Trust® repository was searched on March 11, 2020 for clinical practice guidelines that recommended the use of droperidol 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 droperidol 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 droperidol 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 droperidol 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 droperidol; setting; total number of patients; number of patients who received droperidol; patient population; indication for use of droperidol; dosage form and strength; dose; ROA; frequency and duration of therapy; use of droperidol in a combination product; use and formulation of droperidol in a compounded product; use of droperidol 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 droperidol 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 droperidol: anesthesiology, pain management, primary care and internal medicine, 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 droperidol 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 persons. 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

- Droperidol is available as an FDA-approved product in the nominated dosage form and ROA.
- Droperidol is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for droperidol.
- Droperidol is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium 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]
Droperidol	2.5 mg/mL	Injectable	Injection	Prescription	Approved prior to 1/1/1982

[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]
Droperidol	0.5-5 mg/mL	Solution	Injection, intramuscular, intravenous	Abu Dhabi	Active	–
				Australia	Prescription	5/17/2016
				Belgium	Prescription	1/14/1976
				Ireland	Prescription	2/29/2008
				Namibia	–	8/18/2004
				New Zealand	Prescription	12/31/1969
				Saudi Arabia	Prescription	–
				UK	Prescription	1/28/2008

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

Study selection

Database searches yielded 293 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 214 titles and abstracts were screened. After screening, the full text of 45 articles was reviewed. Finally, 3 studies were included. Forty-two studies were excluded for the following reasons: wrong dosage form or ROA (14 studies); wrong study design (12); droperidol used as an FDA-approved dosage form or ROA (8); language other than English (4); droperidol only mentioned briefly (2); droperidol used as brand or proprietary product (2).

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

Characteristics of included studies

The 3 included studies were published between 2011 and 2015. There were 2 experimental studies, 0 observational studies, 1 descriptive study, and 0 clinical practice guidelines. The 3 studies were conducted in the following countries: Brazil, Turkey, and US.

A total of 368 patients participated in the 3 included studies. The number of patients in each study ranged from 8 to 180.

Outcome measures differed among the included studies and included: pain relief, use of non-intrathecal antiemetics, patient reported incidence of pruritis, intraoperative and post-operative side effects, and time to first pain.

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

Use of droperidol

Eight patients received droperidol as a treatment for nausea and vomiting, administered intrathecally at a starting dose of 22.7 ± 18.6 mcg/day and increased by 15-50 mcg/day as needed. The duration of treatment was not specified. Sixty patients received droperidol as an experimental treatment for pruritis, administered as a one-time 2.5 mg dose. The dosage form and route of administration were not specified. Twenty patients received droperidol as an experimental treatment for analgesia, administered intrathecally at a dose of 1.25 mg. Duration of treatment was not specified.

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

Droperidol was used as a compounded product (refer to Table 9).

In 1 study, the authors' concluding statement recommended droperidol given intrathecally as a safe antiemetic to use with opioid analgesics.[8] In another study, the authors concluded that droperidol was a satisfactory drug to antagonize morphine-induced pruritis.[9] In the last study, the authors' concluding statement did not find a difference among the intrathecal adjuvant agents they used for spinal anesthesia.[10] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

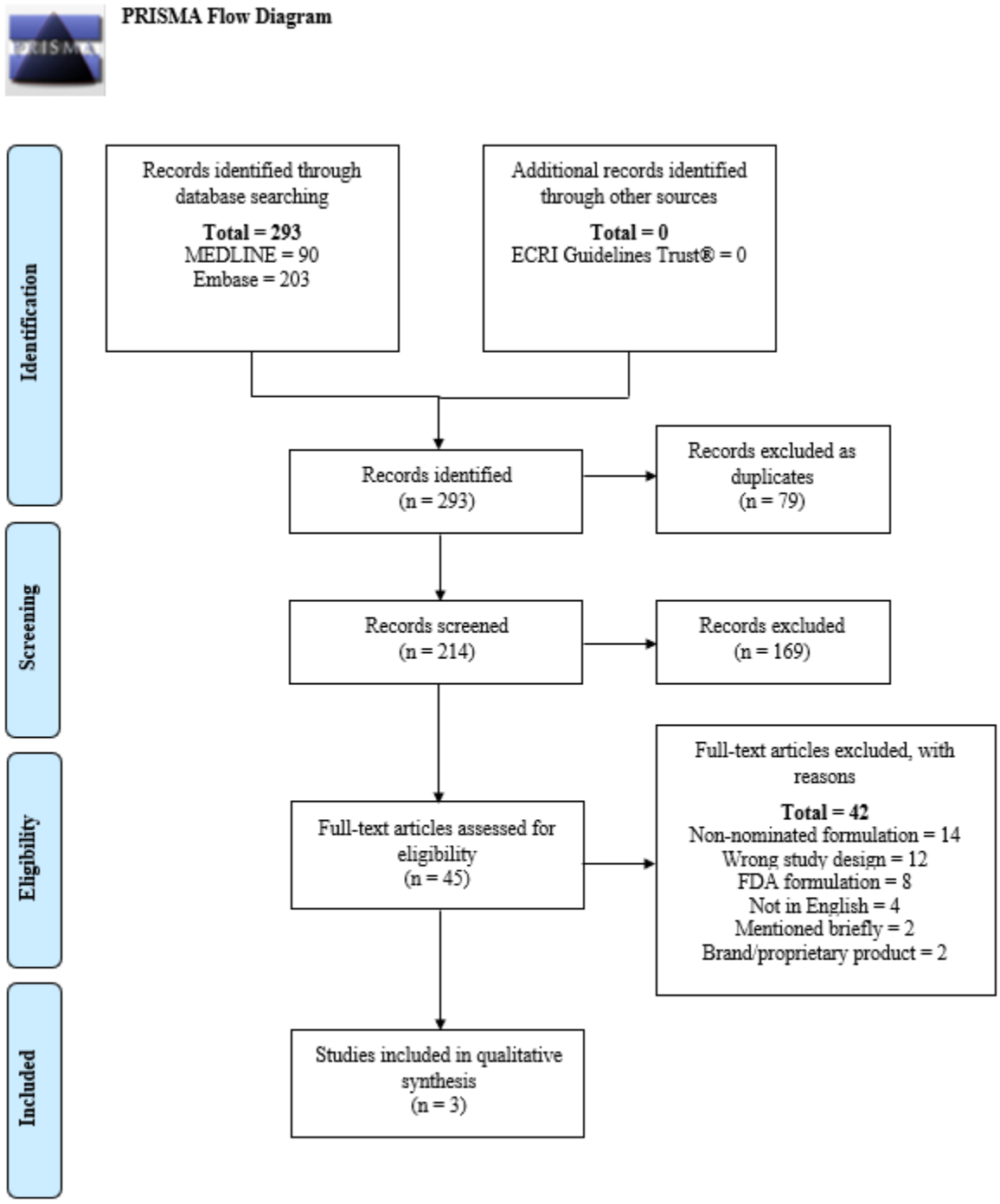
In addition to the 3 included studies, 8 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of droperidol.

Droperidol is a neuroleptic drug that "produces a state of mental detachment and indifference to surroundings with a mild soporific effect although the patient remains fully [cooperative]."[11] It is a potent antiemetic and psycho-sedative that produces an adrenergic blockade and potentiates the action of analgesics.[11] Reported side effects include mental depression, hallucinations, mild agitation, and dyskinesia.[11] In 2001, the FDA issued a black box warning for droperidol that it could increase the chance of QT prolongation and/or torsade de pointes.[8,12] However, there have been a number of sources supporting droperidol's safety and efficiency at recommended doses.[8,13,14] The cases that led to the black box warning also had confounding factors, making it difficult to definitively determine that droperidol was the cause of the reported adverse events.[13]

Droperidol has been shown to reduce the incidence of postoperative nausea and vomiting when used as a premedication, or when administered during general anesthesia, without side effects such as motor dysfunction or neurotoxicity.[15] In a study by Gurses et al, the authors compared the analgesic and adverse effects of tramadol alone and in combination with other drugs for postoperative epidural analgesia.[6] Patients were randomly assigned to 1 of 3 groups: epidural tramadol alone, tramadol and droperidol, or tramadol and clonidine.[6] The authors concluded that epidural tramadol with droperidol or clonidine increased the analgesic duration and that droperidol may be the better alternative when its antiemetic properties and adverse events were considered.[6] In another study looking at long-term use of intrathecal droperidol as an antiemetic, 8 patients with implanted intrathecal narcotic drug delivery systems were given intrathecal droperidol.[8] The authors found that droperidol given at a dose of 5-300 mcg/day intrathecally was a safe antiemetic to use with opioid analgesics.[8]

In a 2003 review on neuraxial opioid-induced pruritus, there was conflicting evidence for droperidol's effectiveness in the treatment or prevention of pruritus.[16] The review mentioned a study done by Horta et al[17] in which 140 patients received epidural anesthesia with morphine, bupivacaine, and epinephrine for cesarean section.[16] Patients were randomly assigned to 4 groups: morphine only, morphine plus 1.25 mg droperidol, morphine plus 2.5 mg droperidol, and morphine plus 5 mg droperidol.[16] The efficacy increased as the dose of epidural droperidol increased but sedation did as well.[16] The study concluded that there was no statistically significant difference between the morphine only group compared to the droperidol groups.[16] A more recent study done by Briao et al in 2015 found that the incidence of moderate to severe pruritis was lower in the droperidol group than that of the ondansetron or metoclopramide groups.[9] They concluded that droperidol is a satisfactory drug to antagonize morphine-induced pruritis.[9] The droperidol dosage form and ROA were not specified in this study.

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[8]	1
Experimental[9,10]	2
Observational	0

Table 4. Number of studies by country

Country	**Number of Studies**
Brazil[9]	1
Turkey[10]	1
US[8]	1
	Total US: 1 Total Non-US Countries: 2

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: Nausea/vomiting					
Ahmad-Sabry and Shareghi., 2012, US[8]	–	8 patients (37.5%, range 54-84 y)	• Droperidol (8)	Pain relief, use of non-intrathecal antiemetics	Droperidol given as a dose of 5-300 mcg/day intrathecally is a safe antiemetic to use with opioid analgesics. The authors suggest a minimal starting dose of 20-30 mcg/day of droperidol and increase by 25-50% on subsequent pump refills until desired effect is achieved.
Indication 2: Pruritis					
Briao *et al.*, 2015, Brazil[9]	Randomized, double-blind trial	180 patients (% male not specified, age distribution reported below*) Droperidol (27.6 y) Metoclopramide (27.1 y) Ondansetron (26.8 y) *Authors did not specify whether the numbers provided for age was the mean.	• Droperidol 2.5 mg (60) • Metoclopramide 10 mg (60) • Ondansetron 8 mg (60)	Patient reported incidence of pruritis (mild, moderate, or severe)	The incidence of moderate and severe pruritis was lower in the droperidol group. Droperidol is a satisfactory drug to antagonize subarachnoid morphine-induced pruritis.

Indication 3: Analgesia/anesthesia					
Yektaz *et al.*, 2011, Turkey[10]	Randomized study	180 patients (35%, range 19-75 y)	• Control: 15 mg 0.5% hyperbaric bupivacaine and 0.5 mL of serum (20) • Intervention: Hyperbaric bupivacaine plus: o Group 1: Hyperbaric bupivacaine 2.5 mg (20) o Group 2: Ketamine 12.5 mg (20) o Group 3: Fentanyl 25 mcg (20) o Group 4: Sufentanil 2.5 mcg (20) o Group 5: Dexmedetomidine 2 mcg (20) o Group 6: Neostigmine 250 mcg (20) o Group 7: Midazolam 500 mcg (20) o Group 8: Droperidol 1.25 mg (20)	Intraoperative and post-operative side effects, time to first pain	Intrathecal adjuvant agents had a similar effect on the characteristics of spinal anesthesia and there were no differences in time to first pain among the agents.

Abbreviations: "–", not mentioned.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Nausea/vomiting[8]	Starting dose: 22.7±18.6 mcg/day Increased by 15-50 mcg/day as needed	–	Solution (preservative-free)	Intrathecal	–

Abbreviation: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Analgesia/anesthesia[10]	1.25 mg	1.25 mg/3 mL	Solution	Intrathecal	–
Pruritis[9]	2.5 mg	–	–	–	Once

Abbreviation: "–", not mentioned.

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

Indication	Compounding Method	Dosage Form	Final Strength
Nausea/vomiting[8]	"Preservative-free compounded antiemetic droperidol in the intrathecal space"	Solution	–

Abbreviation: "–", not mentioned.

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. Eight SMEs discussed droperidol. Amongst the 8 SMEs, there were 1 dentist, 5 medical doctors, 1 nurse practitioner, and 1 pharmacist. The SMEs specialized and/or were board-certified in anesthesiology, critical care, oral and maxillofacial surgery, oncology and hematology, pain medicine, palliative care, and pediatrics, working in academic medical centers and hospital/health systems. The SMEs had been in practice for 6 to 33 years.

Droperidol is an excellent antiemetic but has not been used for about 10-15 years due to the black box warning for risk of QT prolongation. Unless the FDA gets rid of the black box warning, droperidol is unlikely to be used. One SME commented that droperidol is not used because the QT prolongation hits after the patient leaves the hospital. Back in the 1990s, there were reports from patients who received droperidol in procedures and the patients reported that droperidol made them feel weird. Patients have also said, "they'd rather puke" or felt a "sense of impending doom" after the use of droperidol.

Ativan® (lorazepam), Benadryl® (diphenhydramine), Decadron® (dexamethasone), Reglan® (metoclopramide), Zofran® (ondansetron), and/or scopolamine patches are often used to prevent nausea and vomiting. Ondansetron can cause some QT prolongation but not as much droperidol. If the patient has a history of post-operative nausea, then Compazine® (prochlorperazine) and Phenergan® (promethazine) can be given intra-operatively and/or post-operatively. Other ways to help prevent nausea and vomiting are to limit use of narcotics and nitrous oxide in patients and hydrate the patient.

Several SMEs had no experience with droperidol. Others stated that they would not give droperidol intrathecally and/or did not see a need for an intrathecal injection. One SME commented that they have read studies that combined droperidol and fentanyl given IV or IM for sedation but had not personally tried this combination before. One SME who had used droperidol IV in the operating room for nausea used a strength of 2.5 mg/mL or 5 mg/mL for cancer patients who could not keep anything down. This SME could not speak on the need for higher doses as they did not have much experience using the commercially available 2.5 mg/mL product.

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).

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. Two respondents (0.7% of 290 responses, where respondents were allowed to select multiple drug products) obtained droperidol 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 droperidol prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded droperidol

No respondents to survey distributed via professional medical associations

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

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

Droperidol was nominated for inclusion on the 503B Bulks List for treating, among other things, severe pain such as chronic non-malignant pain, and prophylaxis for nausea and vomiting via an IV, IM, and/or intrathecal injection solution up to 2.5 mg/mL. Droperidol is available as an FDA-approved 2.5 mg/mL injection for IV or IM administration; it is also available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium Ireland, Namibia, New Zealand, Saudi Arabia, and UK,

From the literature review and interviews conducted, droperidol is a potent antiemetic. In 2001, the FDA issued a black box warning for droperidol that it could increase the chance for QT prolongation and/or torsade de pointes. With this black box warning in place, droperidol is unlikely to be used. There are disagreements about the black box warning from the literature. Other indications the literature review found for droperidol included pruritis and analgesia/anesthesia.

Several SMEs had no experience with droperidol. Others stated that they would not give droperidol intrathecally and/or do not see a need for an intrathecal injection. One SME had used droperidol IV in the operating room for nausea at a strength of 2.5 mg/mL or 5 mg/mL for cancer patients who cannot keep anything down. Out of the included articles from the literature review, 2 studies used droperidol intrathecally.

Zero people responded to the survey distributed via professional medical associations and available on the project website. Two hundred thirty people responded to the survey distributed via the ASCA. Two respondents reported obtaining droperidol from a 503B outsourcing facility.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to March 10, 2020
- Date last searched: March 12, 2020
- Limits: Humans (search hedge); English language
- Number of results: 90

1	droperidol/	1979
2	deh#drobenz?peridol$.tw.	132
3	deh#drobenzoperiol$.tw.	0
4	droperidol$.tw.	2070
5	droperol$.tw.	0
6	troperidol$.tw.	0
7	or/1-6	2870
8	exp injections, spinal/	15934
9	infusions, spinal/	152
10	spinal$.tw.	262970
11	intraspinal$.tw.	4979
12	epidural$.tw.	41487
13	epi dural$.tw.	5
14	extradural$.tw.	6683
15	extra dural$.tw.	140
16	peridural$.tw.	2056
17	peri dural$.tw.	6
18	intrathecal$.tw.	23414
19	intra thecal$.tw.	73
20	subarachnoid$.tw.	35004

21	or/8-20	342161
22	and/7,21	180
23	exp animals/ not humans/	4676148
24	22 not 23	157
25	limit 24 to english language	90

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 12, 2020
- Limits: Humans (search hedge); English language
- Number of results: 203

1	droperidol'/mj	5037
2	dehidrobenz$peridol*':ti,ab,tn	4
3	dehydrobenz$peridol*':ti,ab,tn	300
4	dehidrobenz$periol*':ti,ab,tn	0
5	dehydrobenz$periol*':ti,ab,tn	0
6	droperidol*':ti,ab,tn	2997
7	droperol*':ti,ab,tn	0
8	troperidol*':ti,ab,tn	0
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	6331
10	intraspinal drug administration'/exp	33019
11	spinal*':ti,ab	361365
12	intraspinal*':ti,ab	6894
13	epidural*':ti,ab	58590
14	epi dural*':ti,ab	40
15	extradural*':ti,ab	9002
16	extra dural*':ti,ab	237
17	peridural*':ti,ab	2996
18	peri dural*':ti,ab	12
19	intrathecal*':ti,ab	34725
20	intra thecal*':ti,ab	229
21	subarachnoid*':ti,ab	49854
22	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	477950

23	#9 AND #22	430
24	[animals]/lim NOT [humans]/lim	6002589
25	#23 NOT #24	394
26	#23 NOT #24 AND [english]/lim	203

Appendix 2.1. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded droperidol. 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)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer droperidol to your patients?

    - Yes
    - No

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

    - Intrathecal injection
    - None of the above

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

    - Nausea and vomiting
    - Severe pain (i.e chronic non-malignant pain)
    - Other (please explain) _____

5. I use compounded droperidol because: (check all that apply)

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

6. Do you stock non-patient-specific compounded chlorpheniramine maleate at your practice?

    - Yes
    - No
    - I'm not sure

7. I obtain compounded droperidol from the following: (check all that apply)

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

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

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

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

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

Appendix 2.2. Survey instrument for Ambulatory Surgery Center Association

Welcome. We want to understand your clinical use of compounded droperidol. 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)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you utilize a 503B outsourcing facility to acquire compounded drugs?
    - Yes. If yes, why. _____
    - No. If no, why not? _____

3. Do you obtain any of the following products from a 503B outsourcing facility? (check all that apply)
    - I do not obtain any compounded dugs from 503B outsourcing facilities
    - Amitriptyline / Ketoprofen / Oxymetazoline
    - Budesonide
    - Calcium gluconate
    - Droperidol
    - Epinephrine
    - Epinephrine for ophthalmic administration
    - Epinephrine / Lidocaine for ophthalmic administration
    - Epinephrine / Bupivacaine / Fentanyl
    - Fentanyl
    - Flurbiprofen
    - Flurbiprofen for ophthalmic administration
    - Hydromorphone
    - Ipamorelin
    - Ketoprofen / Nifedipine
    - Lidocaine / Epinephrine / Tetracaine HCl
    - Meperidine
    - Morphine
    - Naloxone
    - Neomycin
    - Phentolamine
    - Promethazine
    - Remifentanil
    - Sufentanil
    - Tramadol
    - None of the above

4. What type of specialty procedures are performed in your facility? (check all that apply)
    - Dental
    - Dermatology
    - Endoscopy
    - Neurosurgery
    - Obstetrics/gynecology
    - Ophthalmology
    - Otolaryngology
    - Orthopedics
    - Pain
    - Plastics
    - Podiatry
    - 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.