Summary Report

Baclofen

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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
ASCO	American Society of Clinical Oncology
CIPN	Chemotherapy-induced peripheral neuropathy
DMSO	Dimethyl sulfoxide
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
HCl	Hydrochloride
IRB	Institutional Review Board
IV	Intravenous
OTC	Over-the-counter
PACC	Polyanalgesic Consensus Conference
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the US Food and Drug Administration (FDA) in its evaluation of the use of baclofen (UNII code: H789N3FKE8), 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 baclofen 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 baclofen 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 baclofen 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

Baclofen was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA), Fagron Inc., Pentec Health, and the Specialty Sterile Pharmaceutical Society (SSPS). Baclofen was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Baclofen was nominated for use as an intrathecal injection in concentrations ranging from 25-4000 mcg/mL for the treatment of pain and spastic movement disorders, particularly conditions involving spinal cord injury, cerebral palsy, multiple sclerosis, and muscle spasticity due to injury, surgery, or other medical conditions involving muscle tone. Baclofen was also nominated for use as a topical cream, with the strength based on the prescriber's request to treat unknown medical conditions, though the nominator stated that the therapeutic dose is 2% and baclofen is generally used to treat pain.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of baclofen.[6-23]

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

- Intrathecal baclofen has been designated as an orphan drug by the FDA.
- 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.
- Patient need for baclofen provided in combination with other API for intrathecal administration.
- There is a clinical need for intrathecal baclofen to lower the side-effect profile associated with FDA-approved oral medications (such as dantrolene and tizanidine); furthermore, intrathecal baclofen can be administered via a programmable pump to allow preset continuous administration.
- 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.

- 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 baclofen 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 baclofen; name variations of baclofen 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 baclofen. 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: baclofen, and topical administration or form (refer to Appendix 1 for full search strategies). Due to the availability of FDA-approved baclofen products for intrathecal injection, this ROA was not considered for the literature review. Results were limited to human studies in the

English language. Searches were conducted on August 13, 2020. In addition, the ECRI Guidelines Trust® repository was searched on August 13, 2020, for clinical practice guidelines that recommended the use of baclofen and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.3.3 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which baclofen 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, preclinical 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 baclofen was used as: an FDA-approved product in the nominated dosage form, ROA, or combination; a dosage form, ROA, or combination that was not nominated; or an unspecified dosage form or ROA. Studies in which baclofen 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 baclofen; setting; total number of patients; number of patients who received baclofen; patient population; indication for use of baclofen; dosage form and strength; dose; ROA; frequency and duration of therapy; use of baclofen in a combination product; use and formulation of baclofen in a compounded product; use of baclofen 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

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances baclofen was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify medical specialties that would potentially use baclofen. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

In addition to interviews with individual SMEs, a roundtable discussion with pharmacists was held. Participants were identified through outreach to professional associations that would potentially purchase compounded products from outsourcing facilities. A prequestionnaire was distributed to those who agreed to participate to collect information about the types of facilities at which participants worked and the

products they purchased from outsourcing facilities (refer to Appendix 2 for complete survey and *Results of survey* section for results of prequestionnaire). The roundtable lasted 60 minutes and was conducted via Zoom, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

Survey

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

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

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

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

CURRENT AND HISTORIC USE

Results of background information

- Baclofen is available as an FDA-approved product in the nominated dosage form and ROA. Baclofen is also available as an FDA-approved oral tablet and oral solution.
- Baclofen is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for baclofen.
- Baclofen is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, 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]
Baclofen	0.05-2 mg/mL	Injectable	Intrathecal	Prescription	06/17/1992

[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]
Baclofen	0.05-2 mg/mL	Solution Solution for injection/infusion	Intrathecal	Abu Dhabi	Active	–
				Australia	S4 – Prescription-only medicine	03/19/1996
				Belgium	Medical prescription	04/01/1996
				Canada	Prescription	12/31/1994
				Hong Kong	Prescription-only	09/30/2003
				New Zealand	Prescription	07/30/2015
				Saudi Arabia	Prescription	–
				United Kingdom	Prescription-only medication	01/31/2003

Abbreviation: – , not provided.

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

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

Results of literature review

Study selection

Database searches yielded 418 references; 5 additional references were identified from searching ECRI Guidelines Trust® and ClinicalTrials.gov. After duplicates were removed, 358 titles and abstracts were screened. After screening, the full text of 189 articles was reviewed. Sixteen studies were included; after multiple reports of the same study were merged, there were 13 included studies. One hundred seventy-three studies were excluded for the following reasons: wrong study design (130 studies); unspecified dosage form or ROA (27); non-nominated dosage form or ROA (9); wrong drug (4); baclofen mentioned only briefly (3).

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

Characteristics of included studies

The 13 included studies were published between 2005 and 2020. There were 4 experimental studies, 2 observational studies, 3 descriptive studies, and 4 clinical practice guidelines. The 13 studies were conducted in the following countries: Iran, Spain, and US.

A total of 3173 patients participated in the 13 included studies. The number of patients in each study ranged from 1 to 527.

Outcome measures differed among the studies and included: pain score, need for rescue analgesia, change in neuropathy, and functional status.

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

Use of baclofen

One thousand one hundred twenty-four patients received baclofen as a treatment for pain, administered topically 1-4 times per day in concentrations ranging from 0.76%-5%. Duration of treatment ranged from 2 weeks to more than 6 months.

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

Baclofen was used as a compounded product and as a combination product (refer to Tables 8-10).

In 4 studies, the authors' concluding statement recommended the use of topical baclofen for the treatment of pain due to open hemorrhoidectomy, cutaneous leiomyomas associated with Reed syndrome, cervical and/or lumbrosacral radicular pain, and chronic pain.[24-27] In 1 study, the authors concluded that compounded pain creams were no better than placebo creams in the treatment of localized chronic pain.[28] In 3 studies, the authors recommended further research into the use of topical baclofen for the treatment of chemotherapy-induced peripheral neuropathy (CIPN), chronic pain, and provoked vestibulodynia (PV).[7,29,30] In 1 study, the authors did not provide a concluding statement due to their study being underpowered for the treatment of vulvodynia.[31]

Clinical practice guidelines from the Asociación Española de Patología Cervical y Colposcopia (AEPCC) and Spanish Menopause Society (SMS) recommended the use of topical baclofen for the treatment of vulvodynia.[32] Clinical practice guidelines from the American Society of Clinical Oncology (ASCO) stated that compounded topical gels containing baclofen, amitriptyline hydrochloride, and ketamine may be offered to patients with CIPN, given limited alternative options,

but further research is required.[33] Clinical practice guidelines from ASCO also provided a recommendation that compounded creams or gels containing baclofen, amitriptyline, and ketamine be prescribed for cancer survivors with chronic pain.[34] Clinical practice guidelines based on expert opinion reported by Haefner et al. from the US said that a combination of topical amitriptyline and baclofen in a water-washable base has been useful for point tenderness associated with vulvodynia and vaginismus.[35] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 13 included studies, additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of baclofen.

As the "leading cause of years lost to disability worldwide," chronic pain is estimated to affect approximately 31% of the global population.[28] Despite this prevalence, there is a lack of reliable treatments for chronic pain, with first-line medications associated with adverse effects that limit their use.[28] As a result, topical creams have emerged as an alternative to their oral counterparts, in an attempt to limit adverse effects or to overcome a contraindication—such as using nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with chronic kidney disease (CKD).[27,28] The use of topical pain creams may be especially beneficial in military personnel "because opioid therapy may render a service member nondeployable and medications that affect the central nervous system may have a negative effect on judgment and motor skills."[28]

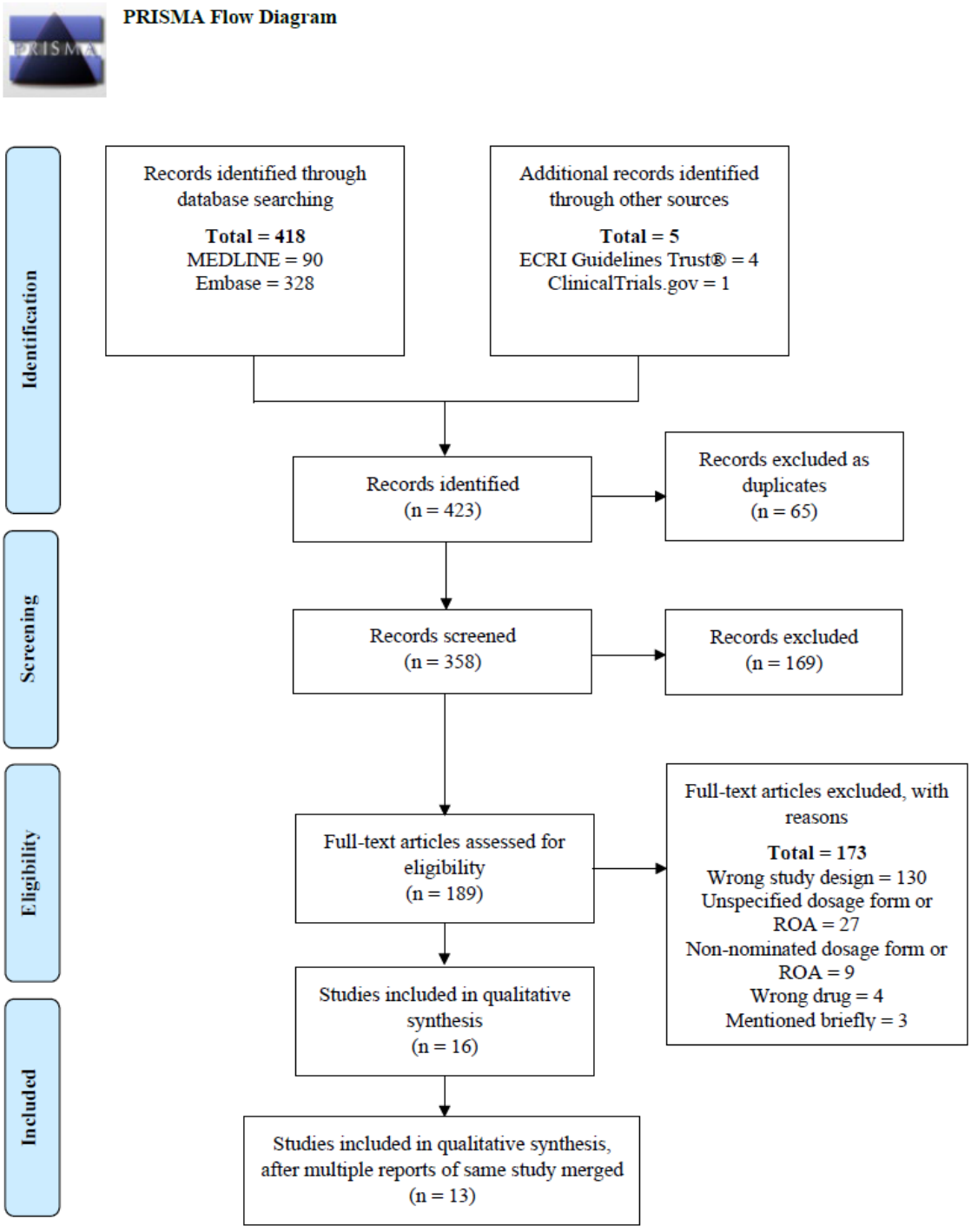
Although there are commercially available topical medications used for pain (such as capsaicin and lidocaine), there is also a market for compounded pain medications that contain multiple active ingredients targeting different mechanisms of action.[25,27,28] Due to increases in the use of compounded pain creams, Brutcher et al conducted a randomized study that found that compounded pain creams were not better than placebo, and their higher cost should limit routine use.[28] However, the authors also said that their study was limited by looking at patients who had failed other treatment options, by not including capsaicin (FDA-approved for both neuropathic and nociceptive pain) or amitriptyline (not approved for chronic pain), and by having a patient population that was relatively young and lacking in other pain conditions for which topical creams are typically used (such as knee osteoarthritis and postherpetic neuralgia).[28] They also said that they were unable to measure adherence due to variations in surface areas requiring treatment, as well as the heterogeneity of the pain conditions that affected their patient population.[28] However, an earlier retrospective evaluation from Somberg and Molnar came to a different conclusion when they compared two compounded creams to commercially available diclofenac (Voltaren®) gel; the diclofenac gel was found to have less efficacy than the compounded creams.[25] The fact that this was an open, retrospective study should be taken into consideration, with the results subject to prescriber bias when selecting study groups. In the review conducted by the National Academies of Sciences, Engineering, and Medicine, the authors concluded that "there is insufficient evidence on the effectiveness of topical baclofen to treat pain when applied to intact skin."[36]

One of the included guidelines for vulvodynia received an update in 2013.[35,37] However, baclofen was mentioned only briefly in this update, with the authors saying "single-arm and retrospective assessments of other compounded topical agents found to reduce vulvodynia (e.g., gabapentin, 2% amitriptyline and 2% baclofen, nitroglycerine, capsaicin, estrogen) should be interpreted with caution."[37]

The FDA has stated that intrathecal drug therapy is indicated for moderate-to-severe trunk and limb pain, as well as intractable pain that has been refractory to conservative treatment attempts.[38] The Polyanalgesic Consensus Conference (PACC) noted that although there is interest in using intrathecal therapy to cover focal extremity pain, support in the literature is lacking, with only anecdotal reports.[38] 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 in which analgesic efficacy with systemic opioid delivery is complicated by intolerable adverse effects.[38]

According to the PACC, intrathecal baclofen is a fourth- or fifth-line medication for intrathecal pain treatment.[38] In the PACC guidelines, the authors note that such medications as baclofen and clonidine are associated with significant withdrawal symptoms in cases of abrupt cessation or interruption of therapy; as a result, prescribers should prepare rescue strategies for this life-threatening situation.[38] Despite the risks associated with the off-label use of intrathecal medications and compounded products (such as infusion system corrosion and device failure), it was suggested that "compounded medications were the de facto standard of care and peer-reviewed literature exists to support the use of both on- and off-label medications."[38] According to an FDA safety communication from November 2018, the agency advises caution and notes that compounded medicines "are not currently approved for use with implanted pumps for intrathecal infusion of pain medicine."[39] Potential safety issues associated with using a non-FDA-approved medication for intrathecal pump administration include pump failure, dosing errors, toxicity to the spinal cord and brain tissue, and formation of granulomas at the tip of the catheter or infusion site.[39]

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[26,27,29]	3
Observational[25,30]	2
Experimental[7,24,28,31]	4
Clinical practice guideline[32-35]	4

Table 4. Number of studies by country

Country	**Number of Studies**
Iran[24]	1
Spain[32]	1
United States[7,25-31,33-35]	11
	Total US: 11 Total Non-US Countries: 2

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication: Pain					
Ala et al., 2020, Iran[24] Ala et al., 2018, Iran[40]	Randomized, double-blind, placebo-controlled clinical trial	60 Patients undergoing open hemorrhoidectomy with third- and fourth-degree hemorrhoids • Baclofen (23.3%, mean 41.54 y +/- 15.54) • Placebo (6%, mean 43.74 y +/- 8.37)	• Baclofen 5% cream (30) • Placebo (30)	Postoperative pain score, the amount of required acetaminophen rescue analgesia over 2 weeks after surgery	"Topical application of baclofen effectively relieves pain after hemorrhoidectomy with minimal side effects."
Barton et al., 2011, US[7] Barton et al., 2009, US[41]	Double-blind, placebo-controlled trial	203 Patients receiving topical therapy for CIPN • Baclofen, amitriptyline, and ketamine (BAK (5%, mean 59.9 y +/- 10.75) • Placebo (41%, mean 62.1 y +/- 10.27)	• BAK pluronic lecithin organogel (PLO) (101) • Placebo (102)	Change in sensory neuropathy subscale as measured by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-CIPN20	"Topical treatment with BAK-PLO appears to somewhat improve symptoms of CIPN. This topical gel was well tolerated, without evident systemic toxicity. Further research is needed with increased doses to better clarify the clinical role of this treatment in CIPN."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Bonham et al., 2015, US[31] Bonham, 2014, US[42]	Double-blind, crossover study	9 Patients with localized provoked vulvodynia (0%, age not specified)	• Amitriptyline 2% and baclofen 2% (7) • Ketoprofen 10% (3) • Ketamine 10% (6) • Loperamide 5% (7) • Gabapentin 6% (8) • Placebo (9) All patients were intended to receive all interventions; 1 was dropped due to noncompliance; ketoprofen was discontinued due to consistent complaints of moderate-to-severe burning	Reduction in daily genital pain scores	"The small number of patients recruited left this study underpowered to uncover significant effects with the medications studied."
Brutcher et al., 2019, US[28]	Double-blind, randomized, parallel study	399 Patients presenting with localized chronic pain of neuropathic, nociceptive, or mixed etiologies • Intervention (49%, median 50.0 y [IQR 38.0-64.0]) • Placebo (49%, median 51.0 y [IQR 39.0-64.0])	• Neuropathic pain: ketamine 10%, gabapentin 6%, clonidine 0.2%, and lidocaine 2% cream (68) • Nociceptive pain: ketoprofen 10%, baclofen 2%, cyclobenzaprine 2%, and lidocaine 2% cream (66) • Mixed pain: ketamine 10%, gabapentin 6%, diclofenac 3%, baclofen 2%, cyclobenzaprine 2%, and lidocaine 2% cream (68) • Placebo (197)	Average pain score 1 month after treatment	"Compounded pain creams were not better than placebo creams, and their higher costs compared with approved compounds should curtail routine use."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Comino et al., 2015, Spain, Spanish Menopause Society (SMS) and the Asociación Española de Patología Cervical y Colposcopia (AEPCC)[32]	Consensus	Patients presenting with vulvodynia requiring treatment	–	–	"For vulvodynia, we recommend the use of lubricants or topical treatments with lidocaine or bupivacaine, amitriptyline, baclofen or triamcinolone."
Farid et al., 2019, US[26]	–	1 Patient with cutaneous leiomyomas associated with Reed syndrome (100%, 39 y)	• Topical cream containing ketamine, diclofenac, baclofen, gabapentin, cyclobenzaprine, and bupivacaine (1)	Patient-reported pain and functional status	"This regimen improved our patient's functional status. Our patient's emotional triggers allowed us to understand the impact of his illness and provided us with a useful metric to measure pain control and functional improvement."
Haefner et al., 2005, US[35]	Guideline	Patients presenting with vulvodynia requiring treatment	–	–	"For some patients with localized pain and vaginismus, a combination of topical amitriptyline 2% (Elavil; AstraZeneca Pharmaceuticals) and baclofen 2% (Lioresol Geigy Novartis Pharmaceuticals, East Hanover NJ) in a water washable base has been useful for point tenderness and vaginismus."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Hershman et al., 2014, US, American Society of Clinical Oncology (ASCO)[33]	Clinical practice guideline	Patients requiring treatment for CIPN	–	–	"On the basis of the paucity of high-quality, consistent evidence, there are no agents recommended for the prevention of CIPN. With regard to the treatment of existing CIPN, the best available data support a moderate recommendation for treatment with duloxetine. Although the CIPN trials are inconclusive regarding tricyclic antidepressants (such as nortriptyline), gabapentin, and a compounded topical gel containing baclofen, amitriptyline HCL, and ketamine, these agents may be offered on the basis of data supporting their utility in other neuropathic pain conditions given the limited other CIPN treatment options. Further research on these agents is warranted."
Nyirjesy et al., 2009, US[29]	Retrospective evaluation	38 Patients with PV (0%, mean 37.8 y +/- 12.4)	• Amitriptyline 2% / baclofen 2% cream (38)	Verbal report, visual analog scales of discomfort with daily and sexual activities, 5-point numerical scales rating change in symptoms	"Our data are limited by the retrospective study design and the lack of a control group. Nevertheless, given a response rate of 71% in women with refractory symptoms and the overall tolerability of this treatment, we suggest that ABC therapy warrants further investigation as a therapy for PV."
Paice et al., 2016, US, ASCO[34]	Clinical practice guideline	Chronic pain management in cancer survivors	–	–	"Recommendation 2.6. Clinicians may prescribe topical analgesics (such as commercially available nonsteroidal anti-inflammatory drugs; local anesthetics; or compounded creams/gels containing baclofen, amitriptyline, and ketamine), for the management of chronic pain. (Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)"

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Safaeian et al., 2016, US[27]	Case series	3 Patients with diagnosis of cervical and/or lumbosacral radicular pain (66.7%, range 39-65 y)	• Topical cream containing diclofenac 5%, ibuprofen 3%, baclofen 2%, cyclobenzaprine 2%, bupivacaine 1%, gabapentin 6%, and pentoxifylline 1% (3)	Patient-reported pain	"This is the first report of the successful treatment of radicular pain with a topical agent. This highlights the need for randomized, prospective study of both single and compounded topical agents for treatment of radicular pain."
Somberg and Molnar, 2015, US[25]	Retrospective review	2177 Patients with chronic pain (38%, mean 39 y ± 9)	• Cream containing flurbiprofen 20%, tramadol 5%, clonidine 0.2%, cyclobenzaprine 4%, and bupivacaine 3% (1141) • Cream containing flurbiprofen 20%, baclofen 2%, clonidine 0.2%, gabapentin 10%, and lidocaine 5% (527) • Voltaren® (diclofenac 1%) gel (509)	Change in numeric pain intensity score	"The analgesic activities of 2 compounded topical creams and Voltaren gel were evaluated in patients with chronic pain. The results indicate that both compounded creams provide significantly more pain relief than Voltaren gel."
Somberg and Molnar, 2015, US[30]	Retrospective study	283 Patients with chronic pain (41%, age not specified)	Two creams were evaluated, both containing ketamine 10%, baclofen 2%, gabapentin 6%, amitriptyline 4%, bupivacaine 2%, clonidine 0.2% and: • No nifedipine (78) • Nifedipine 2% (205)	Change in numeric pain intensity score	"The creams were equally effective in diabetic neuropathy, neuropathic pain, or other chronic pain states. We conclude that both creams provided excellent pain relief in the majority of the patients studied and may be a useful modality for pain therapy."

Abbreviations: –, not provided; ABC, amitriptyline and baclofen cream; BAK, baclofen, amitriptyline, and ketamine; CIPN, chemotherapy-induced peripheral neuropathy; EORTC QLQ, European Organization for Research and Treatment of Cancer quality-of-life questionnaire; HCL, hydrochloride; IQR, interquartile range; PLO, pluronic lecithin organogel; PV, provoked vestibulodynia.

[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Pain[7,25-31,33-35]	Apply 1-4 times per day	0.76%-2%	Cream, gel	Topical	2 weeks-3 months 5.4 months +/- 4.8 6.4 months +/- 5.1
	Apply 0.5 mL 1-3 times per day	2%	Water washable base	Topical	–
	Apply a pea-sized amount twice daily	2%	Cream	Topical	4-6 weeks
	Apply 1-2 g 3-4 times per day	2%	Cream	Topical	3-4 months

Abbreviation: –, not provided.

Table 7. Dosage by indication – non-US countries

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Pain[24,32]	Apply every 12 hours	5%	Cream	Topical	2 weeks

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Baclofen 4% / Amantadine HCl 8% / Amitriptyline HCl 2% / Clonidine HCl 0.2% / DMSO 5% / Gabapentin 5% / Ketoprofen 10% / Lidocaine HCl monohydrate 5% – topical cream	0
Others found in literature	Baclofen 2% / Amitriptyline 4% / Bupivacaine 2% / Clonidine 0.2% / Gabapentin 6% / Ketamine 10% / Nifedipine 2% – topical cream[30]	1
	Baclofen 2% / Bupivacaine 1% / Cyclobenzaprine 2% / Diclofenac 5% / Gabapentin 6% / Ibuprofen 3% / Pentoxifylline 1% – topical cream[27]	1
	Baclofen 2% / Amitriptyline 4% / Bupivacaine 2% / Clonidine 0.2% / Gabapentin 6% / Ketamine 10% – topical cream[30]	1
	Baclofen / Bupivacaine / Cyclobenzaprine / Diclofenac / Gabapentin / Ketamine – topical cream[26]	1
	Baclofen 2% / Cyclobenzaprine 2% / Diclofenac 3% / Gabapentin 6% / Ketamine 10% / Lidocaine 2% – topical cream[28]	1
	Baclofen 2% / Clonidine 0.2% / Flurbiprofen 20% / Gabapentin 10% / Lidocaine 5% – topical cream[25]	1
	Baclofen 2% / Amitriptyline 2% – topical cream,[31] water-washable base[35]	2

Abbreviations: DMSO, dimethyl sulfoxide; HCl, hydrochloride.

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Pain[7,25,27-31,35]	2005-2019	"Compounded at Gateway HealthMart Pharmacy Laboratory in Bismarck, North Dakota"	Gel	10 g/1.31 g
		"Compounded in Cetaphil™"	Cream	2%
		"Creams were formulated by using a lipophilic-based carrier (Transdermal Pain Base [Medisca]) and placed through the compounding mill twice to decrease particle size, which enhances penetration."	Cream	2%
		"The topical compound was prepared by one of two established compounding pharmacies"	Cream	6%
		"Compounded topical creams"	Cream	10%
		"Compounded topical cream"	Cream	6%
		"A compounding pharmacy is used to formulate these topical medications."	Water-washable base	2%
		Combined amitriptyline and baclofen with enough ethoxydiglycol to form it into a smooth paste; incorporated lipoderm cream into paste; ran the cream through an ointment mill	Cream	2%

Table 10. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Pain[24]	• Aqueous phase prepared by dissolving preservatives (paraben and methyl paraben) and borax in autoclaved water with homogenizer and heating at 70 °C. • Oil phase prepared by mixing liquid white paraffin, baclofen powder, and beeswax and heating at 70 °C. • Aqueous phase was added to oil phase, mixed continuously as allowed to cool.	Cream	5%

Results of interviews

One hundred ninety-nine SMEs were contacted for interviews; 63 agreed to be interviewed, and 136 declined or failed to respond to the interview request. Six SMEs discussed baclofen. Among these 6 SMEs, there were 3 medical doctors, 2 doctors of podiatric medicine, and 1 nurse practitioner. The SMEs specialized and/or were board-certified in dermatology, infectious disease, obstetrics and gynecology, and pain management, working in academic medical institutions and private practice. The SMEs had been in practice for 3 to 56 years. Additional information was collected as part of the Expanded Information Initiative, referred to as Phase 3—a project in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

Four SMEs commented on the use of compounded topical pain products, though 3 of those SMEs did not use these products. One SME used baclofen frequently but only the oral formulation. The 1 SME that did utilize topical pain products mentioned that these topical formulations are never first-line options and are used only if the patient asks for a product that they do not have to take by mouth, or if the patient has tried topical lidocaine or Voltaren® (diclofenac) gel with no relief.

When determining the appropriate formulation, one SME commented that the differing pathologies of pain with which a patient presents will guide the selection of ingredients. Typically, each formulation has three or four APIs, allowing them to utilize multiple mechanisms of action to treat the patient's pain, or to treat pain of multiple etiologies (for example, neuropathic and inflammatory). Baclofen is typically added for patients with osteoarthritis and muscle spasms. Baclofen is also used for patients with myofascial pain, along with a variety of other topical medications, such as local anesthetics, anti-inflammatories, or clonidine. The SME noted that "really you can put everything but the kitchen sink in there hoping that it would help." Topical formulations are beneficial in patients with comorbidities that prevent the use of oral medications. The SME provided the example of a patient with arthritis and kidney disease who is, therefore, unable to take an oral nonsteroidal anti-inflammatory drug (NSAID). The SME stated, "If you can get everything in a topical form and they don't have to take it orally, obviously that would be best for the patient if it actually works for them." This SME added that they prefer to minimize the number of oral medications that a patient takes in order to avoid unwanted adverse effects.

Another SME stated that they never use topical compounded pain products, claiming "and my patients who have been using them from other doctors have only succeeded in getting their insurance companies ripped off for hundreds, maybe thousands, of dollars." Typically, these products are being used for patients with neuropathic or arthritic pain, and "they're in legitimate pain, no question about it, but I cannot grasp these combinations of drugs." The SME had concerns about the use of combination topical pain medications, stating, "One drug's active ingredient may not be soluble in the vehicle of another."

Two SMEs commented on the use of baclofen to treat vulvodynia. Vulvodynia is a clinical diagnosis with a variety of different forms. One of the SMEs said, "I personally divide it up into those women who have got an inflammatory component and another group of women where there's a neuropathic component. Neuropathic, in other words, we're into nerve-induced, not inflammational, pain. And some of the women have significant skeletal muscle spasm and not smooth muscle spasm, where they can actually get what is called vaginismus, where they actually get contraction of the skeletal muscles in the sling, in the pelvic muscles of the floor." As a result, management depends on the different elements involved in each patient's etiology. Vulvodynia patients who experience significant local inflammation may undergo surgery to remove the inflamed vestibule. However, not everyone undergoes surgery, and even the patients who eventually undergo surgery might wait months or years before receiving the appropriate surgery. As a result, they may use compounded products to treat the problem in the meantime. Although some products contain lidocaine, an SME cautioned, "The problem with the use of lidocaine in a topical

product is that you often get reactive pain or pain that gets worse when it [lidocaine] wears off. So, you get some relief from, say, burning and pain. And then you get relief for a couple of hours or a few hours, and then you get worse off when you get a second round of pain. So, lidocaine is a somewhat problematic product."

In many cases, products for vulvodynia will contain gabapentin or similar agents, varying from 3%-5% concentrations, either alone or in combination with amitriptyline. According to an SME, "Amitriptyline and the gabapentin are really used for people whose pain is a major component, especially when it's unprovoked pain. But they may be also used when [the pain is] provoked. And both of [the medications], either used alone or in combination, are often used together with baclofen. And baclofen is a muscle relaxer. So, you can get one, two, you've got now five possibilities [of medicine combinations] ... maybe 10 if you're using different concentrations with each." These agents are applied once or twice daily, but there are not many studies determining the most beneficial combinations.

Another SME commented that gabapentin can be compounded in concentrations up to 10%, but this SME predominately uses gabapentin 6% in combination with amitriptyline and baclofen. This combination can treat pain through different mechanisms. Some products might come with additional estrogen in the form of either estradiol or estriol, with the SME noting, "Estriol is a little bit less potent than estradiol. But it's better tolerated." Sometimes, the SME adds estrogen or testosterone as a solo product, or they combine the hormone with the other active ingredients. Topical diazepam has also been used, but it is not commonly applied, and "if diazepam works, you don't know how much of it is a local effect versus how much is due to absorption and having a central effect."

Another SME stated, "Apart from the potential for local burning, the absorption [of topical diazepam] is so low, you have no systemic side effects," continuing that the topical medications are "very relatively safe." When asked about the efficacy of topical products, one SME said, "If they didn't work at all, they wouldn't sell. So, you never know how much of it is placebo effect. You'll never know how much of it has helped." There is not much published research on this matter, and there is debate regarding whether the studies that have been completed treated the right patient population.

There are challenges with insurance coverage and payment, with one SME commenting that most of their patients are on Medicare or Medicaid and have difficulties being able to afford the compounded products, noting, "A few of them [compounding pharmacies] are now taking Medicare, but most of them won't take Medicaid…so obviously payment is key because they charge." The SME continued that a patient had informed them that the pharmacy was charging "about $700 for a small can or jar." Another SME said, "I can tell you most of the patients who you prescribe these for, their insurance companies will not cover any of this stuff, most of this stuff. Women are very desperate. And there's a placebo effect. But you're also giving them confidence, you're reassuring them. You're giving them a shoulder to cry upon. You're reassuring them. You're giving them hope. And you don't know how much all of that counts in your response. And it's probably very important."

As part of Phase 3, 1 nominator provided additional information regarding the multi-ingredient products contained within the baclofen nomination.

Baclofen 4% / amantadine HCl 8% / amitriptyline HCl 2% / clonidine HCl 0.2% / gabapentin 5% / ketoprofen 10% / lidocaine HCl 5% / dimethyl sulfoxide (DMSO) 5% will be compounded as a topical cream to treat neuropathic pain, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. None of the active ingredients contained within this product are available as an FDA-approved drug intended for topical administration. This product will be compounded without the following inactive

ingredients: silicon dioxide, methylparaben, titanium dioxide, talc, lactose, mineral oil, magnesium stereate, propylene glycol, hypromellose, and propylparaben, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include effects as an allergen (classified as toxic or harmful), a human endocrine disruptor, a human immune toxicant, and a possible human carcinogen. Baclofen is added to treat spasticity, amantadine for pain management, amitriptyline for its ability to inhibit both serotonin and noradrenaline reuptake, clonidine for its analgesic effects, gabapentin to mediate pain, ketoprofen for its anti-inflammatory properties, and lidocaine for its analgesic properties.

This product is needed because it will result in a clinical difference to patients, as it does not include harmful excipients found in FDA-approved drug products. Furthermore, this combination of active and inactive ingredients cannot be found in any commercially available formulations.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. Forty-three participants attended the event; refer to Table 15 for characteristics of the facilities that the participants represented. A prequestionnaire was also distributed to participants; refer to Tables 15-18 for results of the prequestionnaire.

While a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtained varied from less than 1% to the majority of compounded products used at one participant's facility. A participant stated, "we have this method that we use where if we can buy it commercially ready to administer, we do that. If we can't buy it in that format, then we buy it in a vial, for example, that can be snapped into a Mini-Bag Plus, because we're a Baxter house, as a second preference. If we can't buy it in either of those two formats and we can get it from a 503B, then we do that. And our last resort is compounding internally." Two participants commented that they will not outsource a product unless 2 outsourcing facilities that they contract with are able to compound the product. This redundancy will allow for a quick flip to the other outsourcing facility if there is an issue with a product compounded from 1 outsourcing facility, minimizing the impact to the participant's facility.

Participants were asked to discuss the decision-making process used at their facility to determine what products to obtain from an outsourcing facility. One major theme that emerged from this discussion was that many of the products purchased from outsourcing facilities are used in critical care areas, like emergency departments and operating rooms. Participants commented that outsourcing facilities are able to provide ready-to-use products that have longer beyond-use dates compared to products compounded in-house, allowing these products to be stocked in automated dispensing cabinets in these units. One participant commented that "we're always going to outsource a PCA [patient-controlled analgesia] syringe because we can store it in a Pyxis machine versus us making it and storing it in a fridge." Another participant commented on the benefits of storing medications in an automated dispensing cabinet, stating that "operationally, if you have a stat medication or something that needs to be delivered within 10 to 15 minutes, if you're looking at us doing it, you're looking at a 5-minute gown and glove. If we don't have somebody in the IV [intravenous] room, if you're doing <797> right, it's 5 minutes. It's 4 minutes to tube it. It's 3 minutes to make it, and then you have a dosage system or a camera system, a few minutes more. We are not able to meet that need or they're just contaminating the IV room if they are trying to do it."

Having ready-to-use products available also minimizes the need for compounding and product manipulations to occur on the floor. This can be especially beneficial in children's hospitals as they face a unique need in that they are already having to perform a lot of manipulations to products due to a lack of concentrations or sizes available. One participant commented that "at baseline, already, we manipulate about 80% of what we dispense to patients" and another stated that "there's a number of drugs that

require additional manipulation to get them to a concentration that's appropriate for kids." One participant stated that "we're trying to minimize compounding, expedite actual therapies to patients in that setting [operating room], minimize manipulations as much as possible." Similarly, in the emergency department, one participant stated they prefer ready-to-use products for some floor-stock items, like vasopressor infusions, to prevent compounding from occurring on the floor and another commented that "we absolutely buy as many pressor drips as we can." One participant remarked that they have received requests from anesthesiologists for products that are commercially available in vials that require manipulation prior to administration to be purchased as syringes from outsourcing facilities, stating that "they would prefer to have a syringe form."

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

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

One participant also commented on the impact that The Joint Commission has had on pushing pharmacies to obtain products from outsourcing facilities. The 2018 medication management standard MM.05.01.07 was intended to move IV admixture preparation out of the nursing unit. This forced pharmacies to

consider strategies to make IV admixtures available for use on the floor. Additionally, NPSG.03.04.01 states that all medications and solutions should be adequately labeled, including in the operating room and other settings in which procedures are performed. USP <795> and <797> are applicable in operating room settings, stating that products should be labeled and used within 1 hour, which may be problematic if syringes are drawn up at the beginning of the day and cases are canceled or delayed. The participant also commented on the cost related to purchasing premade products from manufacturers, stating that "predatory pricing on premixes is present in the market."

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products used. However, the products used in a facility are often developed in-house over decades based on physician and nurse requests, and more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, "these practices had evolved somewhat disparately. Even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines." This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, "I think we made 9 different epidural concentrations, all driven by anesthesia, and they want what they want, and 503Bs may not offer that. No one else in the country is buying that same concentration; a 503B isn't going to go through the expense of adding that to their product list." The participant also said that "similar with the ADCs [automated dispensing cabinets], we've run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, 'no, we can't have it, and that's too big, it won't fit, we want it in this format' and then we're stuck again because there's no 503B offering a format during that shortage that fits where it needs to go. Then we're stuck in sourcing." Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that "3% saline, for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We're either going to draw that out or we're sending it to the ER with stickers all over it saying only give 150 [mL]." The participant continued that "it would be great if the FDA could look at the size of the container that they're approving and whether that's a realistic dose: is it a unit dose, or isn't it?"

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

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

A few participants commented on the need for preservative-free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative-containing product. So, there is a need for this product to be compounded from API as a preservative-free product. One participant stated that "if there's not a preservative-free containing option, it really should be something that should be able to be compounded from bulk . . . especially for the pediatric patient population." However, another participant from a children's hospital said that they have never needed to use an outsourcing facility for preservative-free products. Preservative-free is also an issue for ophthalmic products; however, one participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing facilities but are not able to, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products, but when they reviewed the facilities, they did not pass their internal quality standards; one facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams due to the potential cross-reactivity in patients with allergies. One participant stated that there are some cephalosporins they would like to obtain from an outsourcing facility but cannot because "they would have to build a separate cleanroom with a dedicated HVAC [heating, ventilation, and air conditioning], so you're talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn't there." Another participant stated that the concentrations required for ophthalmic antibiotics are not available, but the labor and risk of compounding these products in-house are not worth it.

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

inpatient pharmacy is often asked to take on this role but "you don't have the space or the staff to do that."

Based on the responses to the prequestionnaire (refer to *Results of survey*), participants were asked questions regarding specific products obtained from outsourcing facilities. Several participants reported using alum (aluminum potassium) as a bladder irrigation for hemorrhagic cystitis refractory to other treatment options. Participants commented that this is high-risk compounding; they purchase alum from an outsourcing facility because they do not perform high-risk compounding in their facility. One participant commented that their policy states that high-risk compounding is not allowed except for alum. This participant wanted to move away from compounding alum in-house and stated that the addition of aluminum potassium to the bulks list might allow this to happen. Another participant had compounded alum in-house from nonsterile ingredients; however, there had been challenges with crystallization after storage. A few participants commented that there is a sterile alum powder available, which they purchase to compound in-house. One participant had concerns regarding this powder, stating that "I've talked to that company, but I've had some concerns for them because they don't sell it as a drug. The owner was selling you a chemical, we're selling you a bulk API. It's just sterile. They were fuzzy and I never followed up, but when I asked about their process for verifying the sterility, as you would with a sterile product—we do USP <71> Sterility Testing—they couldn't really give me an answer. They just say they tested for sterility." The participants commented that alum is only needed a few times a year. However, as one participant observed, "When you need it, it's an emergency," and another noted that it "is a challenge for anybody who has cyclophosphamide-induced hemorrhagic cystitis." As a result, one participant maintains a small inventory of alum product that is purchased from an outsourcing facility but "more times than not, they go unused and expire." Another stated that they do not keep it in stock because there is a minimum purchase and there are only a few cases a year for which they need to use alum. The participant had it stat shipped when needed. Another participant stated that "we had a meeting with the head of urology who was baffled, why they're even ordering it. He was like, 'this is . . . old, really old. I don't even know why we're using it' and basically approved for us to not even make it anymore for now."

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

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

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

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

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

Results of survey

Two people responded to the survey that was distributed via professional medical associations and available on the project website; refer to Table 11 for respondent characteristics.

Among respondents, 2 (100%) used baclofen. Respondents used baclofen as a topical product (1, 50% of respondents) and as an unknown ROA and dosage form (1, 50%). The 1 respondent who used topical baclofen utilized it for pain as well as in combination with other APIs (1, 50%) (refer to Table 12). The

respondent did not provide a reason for using compounded baclofen; nor did they state whether they stocked non-patient-specific compounded baclofen at their practice, or how they obtained compounded baclofen (refer to Tables 13 and 14).

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 2.2 for survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 15 for respondent characteristics. Among respondents, 35 (81% of 43 total respondents) utilized outsourcing facilities to obtain drug products, 4 (9%) did not utilize outsourcing facilities, and 4 (9%) did not respond to this question.

Twenty-seven respondents (19% of 143 responses, in which respondents were allowed to select multiple reasons) obtained drug products from outsourcing facilities due to a need for ready-to-use products, and 20 respondents (14%) obtained drug products from outsourcing facilities due to backorders (refer to Table 16).

Fourteen respondents (31% of 45 total responses, in which respondents were allowed to select multiple types) obtained nonsterile products from outsourcing facilities, and 31 (69%) obtained sterile products from outsourcing facilities. Refer to Table 17 for the categories of products obtained from outsourcing facilities.

Four respondents (4% of 108 responses, in which respondents were allowed to select multiple drug products) obtained baclofen from a 503B outsourcing facility (refer to Table 18).

Table 11. Characteristics of survey respondents

No survey respondents provided this information

Table 12. Conditions for which baclofen prescribed or administered

Condition	Responses, n (N=2)
Pain	1
No Response	1

Table 13. Reasons for using compounded baclofen

No survey respondents provided this information

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

No survey respondents provided this information

Table 15. Demographics of prequestionnaire respondents' facilities

Type of Facility	**Responses, n (N=102)[a]**
Academic medical center	15
Acute care hospital	16
Children's hospital	8
Community hospital	11
Critical access hospital	2
Dialysis center	2
Federal government hospital	4
Health system	15
Inpatient rehabilitation center	4
Long-term acute care hospital	3
Outpatient surgery center	6
Rural hospital	2
Skilled nursing facility	0
Specialty hospital[b]	4
Trauma center	5
Urban hospital	5
Number of Beds	**Responses, n (N=39)**
< 50	4
50-99	3
100-199	1
200-299	4
300-399	5
400-599	3
> 600	19

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

Table 16. Reasons for obtaining products from outsourcing facilities

Categories	Responses, n (N=143)[a]
Backorders	20
Convenience	19
Cost	10
Need for concentrations not commercially available	19
Need for multi-ingredient products not commercially available	10
Need for preservative-free products	3
Need for ready-to-use products	27
No FDA-approved product available	7
No onsite compounding facility	1
Onsite compounding facility not equipped to compound all necessary products	19
Other[b]	8

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

Table 17. Categories of products obtained from outsourcing facilities

Categories	Responses, n (N=142)[a]
Cardioplegic solutions	14
Dermatologic preparations	6
Dialysate solutions	0
Fluids	8
Ophthalmic preparations	10
Patient-controlled analgesia	20
Ready-to-use anesthesia syringes	25
Ready-to-use antibiotic syringes and/or bags	14

Ready-to-use electrolyte solutions	5
Ready-to-use vasopressor solutions	18
Total parenteral nutrition solutions	16
Other[b]	6

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

Table 18. Products obtained from an outsourcing facility

Product	**Responses, n (N=108)[a]**
Acetylcysteine	1
Adenosine	2
Aluminum potassium sulfate	2
Aspartic acid	0
Atenolol	0
Atropine	9
Baclofen	4
Betamethasone	0
Biotin	0
Bupivacaine	8
Calcium chloride	1
Caffeine sodium benzoate	0
Cholecalciferol	1
Chromium chloride	0
Clonidine	0
Dexamethasone sodium phosphate	0
Diclofenac	0
Gentamicin	0

Glycerin	1
Hydroxyzine	0
Ketamine	14
Levocarnitine	0
Lidocaine	8
Lorazepam	2
Magnesium sulfate	4
Manganese chloride	0
Methylprednisolone	0
Midazolam	15
Mupirocin	1
Norepinephrine	15
Ondansetron	0
Phytonadione	0
Potassium chloride	0
Potassium phosphate	0
Prilocaine	0
Proline	0
Propranolol	1
Ropivacaine	6
Sodium chloride	0
Sodium citrate	3
Sodium phosphate	0
Tetracaine	2
Triamcinolone acetonide	0
Tropicamide	0

None of the above	8

[a]Respondents were allowed to select multiple products.

CONCLUSION

Baclofen was nominated for inclusion on the 503B Bulks List as an intrathecal injection and topical cream to treat pain and spastic movement disorders, particularly conditions involving spinal cord injury, cerebral palsy, multiple sclerosis, and muscle spasticity due to injury, surgery, or medical conditions involving muscle tone. Baclofen is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, New Zealand, Saudi Arabia, the UK, and the US.

From the literature review, 13 studies were included. The studies utilized baclofen as a topical product to treat pain. Four studies recommended the use of topical baclofen for certain pain conditions, and 4 studies stated that additional studies were needed prior to recommendation. Clinical practice guidelines from AEPCC and SMS recommend topical baclofen for the treatment of vulvodynia. Additionally, guidelines constructed from expert opinion stated that topical baclofen has been useful in patients with vulvodynia and vaginismus. The ASCO clinical practice guidelines state that compounded products with baclofen could be considered to treat CIPN and cancer survivors who have chronic pain, but ASCO recommends that additional research be conducted.

According to the interviews, 3 SMEs had not used topical baclofen, with 1 SME commenting that they use baclofen frequently but only as the oral formulation. One SME had utilized topical baclofen for the treatment of pain but stated that topical pain formulations are typically not first-line therapy. Although there is minimal literature available regarding the effectiveness and ideal formulation of topical baclofen, 2 SMEs reported that topical baclofen can be used to treat vulvodynia, generally in combination with amitriptyline and gabapentin.

Based on the survey responses, 2 of 2 respondents used baclofen. Baclofen was used as a topical product to treat pain. According to the prequestionnaire, 4 respondents obtained baclofen 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 nonindexed citations and daily 1946 to August 12, 2020
- Date last searched: August 13, 2020
- Limits: Humans (search hedge); English language
- Number of results: 90

1	baclofen/	5606
2	bac?ofen$.tw.	7097
3	bac?ophen$.tw.	24
4	bak?ofen$.tw.	1
5	bak?ophen$.tw.	0
6	or/1-5	8085
7	administration, topical/	38,430
8	administration, cutaneous/	22,069
9	skin absorption/	11,688
10	topical$.tw.	105,381
11	transcutaneous$.tw.	14,432
12	epicutaneous$.tw.	2010
13	transdermal$.tw.	14,590
14	((cutaneous$ or dermal$ or skin) adj3 (absorb$ or absorpt$)).tw.	3202
15	emulsions/	17,950
16	exp gels/	51,921
17	suspensions/	7750
18	liniments/	123
19	ointments/	12,790
20	powders/	13,851

21	skin cream/	1032
22	emulsion?.tw.	33,104
23	suspension?.tw.	108,971
24	gel?.tw.	308,110
25	liniment?.tw.	145
26	ointment?.tw.	11,849
27	salve?.tw.	341
28	paste?.tw.	12,471
29	unguent$.tw.	113
30	lotion?.tw.	2306
31	cream?.tw.	18,935
32	powder?.tw.	68,130
33	or/7-32	722,566
34	and/6,33	132
35	exp animals/ not humans/	4,724,897
36	34 not 35	92
37	limit 36 to english language	90

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: August 13, 2020
- Limits: Humans (search hedge); English language
- Number of results: 328

1	baclofen'/de	18,288
2	bac$ofen*':ti,ab,tn	9755
3	bac$ophen*':ti,ab,tn	38
4	bak$ofen*':ti,ab,tn	3
5	bak$ophen*':ti,ab,tn	0
6	#1 OR #2 OR #3 OR #4 OR #5	19,083
7	topical drug administration'/de	82,575
8	cutaneous drug administration'/de	662
9	transdermal drug administration'/de	9050
10	skin absorption'/de	8046
11	topical*':ti,ab	14,9364
12	transcutaneous*':ti,ab	19,376
13	epicutaneous*':ti,ab	3403
14	transdermal*':ti,ab	21,285
15	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp*)):ti,ab	4446
16	cream'/de	9431
17	gel'/exp	76,899
18	liniment'/de	251
19	lotion'/de	2861
20	ointment'/de	17,908
21	paste'/de	2518
22	powder'/exp	36,699

23	salve’/de	166
24	suspension’/exp	111,771
25	cream$’:ti,ab	29,644
26	emulsion$’:ti,ab	45,043
27	liniment$’:ti,ab	234
28	lotion$’:ti,ab	4004
29	ointment$’:ti,ab	21,585
30	paste$’:ti,ab	14,964
31	powder$’:ti,ab	86,794
32	salve$’:ti,ab	475
33	suspension$’:ti,ab	144,867
34	unguent*’:ti,ab	240
35	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	687461
36	#6 AND #35	426
37	[animals]/lim NOT [humans]/lim	6,074,175
38	#36 NOT #37	357
39	#36 NOT #37 AND [english]/lim	328

Appendix 2.1. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

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

2. Do you prescribe or administer baclofen to your patients?
    - Yes
    - No
3. Do you prescribe or administer baclofen by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Topical products including but not limited to cream, emulsion, gel, ointment, solution, suspension
    - None of the above
4. I prescribe or administer baclofen for the following conditions or diseases: (check all that apply)
    - Pain
    - Other (please explain) _____
5. I prescribe or administered compounded baclofen in combination with other active pharmaceutical ingredients.
    - Yes
    - No
6. I use compounded baclofen because: (check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
    - Patient allergies prevent me from using commercially available products (please explain) _____
    - Patient conditions prevent me from using commercially available products (please explain) _____
    - I am not aware of any commercially available products containing baclofen
    - Other (please explain) _____
7. Do you stock non-patient-specific compounded baclofen at your practice?
    - Yes
    - No
    - I'm not sure
8. I obtain compounded baclofen 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) _____

9. 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) _____
10. What degree do you hold? (check all that apply)
    - Doctor of Medicine (MD)
    - Doctor of Osteopathic Medicine (DO)
    - Doctor of Medicine in Dentistry (DMD/DDS)
    - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - Naturopathic Doctor (ND)
    - Nurse Practitioner (NP)
    - Physician Assistant (PA)
    - Other (please describe) _____

Appendix 2.2. Survey instrument for pharmacy roundtable prequestionnaire

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

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

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

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

Appendix 3. Survey distribution to professional associations

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

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