Summary Report

Gabapentin

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

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

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of gabapentin (UNII code: 6CW7F3G59X), 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 gabapentin 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 gabapentin 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 gabapentin 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

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

Gabapentin was nominated for vulvodynia via topical and vaginal cream (3-10%). It was also nominated to treat an unspecified medical condition, but the nominators said that it is generally used to treat pain.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of gabapentin.[6-13]

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

- The oral formulations of gabapentin are associated with cognitive side effects and patients show low tolerance to the oral dosing necessary to treat vulvodynia; the cream is well-tolerated with significant relief and few side effects.
- 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.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of gabapentin 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 gabapentin; name variations of gabapentin 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 gabapentin. 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: gabapentin, and topical or vaginal administration or form (refer to Appendix 1 for full search strategies). Results were limited to human studies in English language. Searches were conducted on August 20, 2020. In addition, the ECRI Guidelines Trust® repository was searched on August 20, 2020 for clinical practice guidelines that recommended the use of gabapentin 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 gabapentin 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 gabapentin 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 gabapentin 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 gabapentin; setting; total

number of patients; number of patients who received gabapentin; patient population; indication for use of gabapentin; dosage form and strength; dose; ROA; frequency and duration of therapy; use of gabapentin in a combination product; use and formulation of gabapentin in a compounded product; use of gabapentin 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 gabapentin 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 gabapentin. 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 gabapentin 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

- Gabapentin is not available as an FDA-approved product in the nominated dosage form and ROA. Gabapentin is available as an FDA-approved oral capsule, oral solution, and oral tablet (regular and extended release).
- Gabapentin is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for gabapentin.
- Gabapentin is not available in the nominated dosage form and ROA in any of the national registries searched.

Table 1. Currently approved products – US

No approved products in the US

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

No approved products in the selected non-US countries and regions

Results of literature review

Study selection

Database searches yielded 965 references; 8 additional references were identified from searching ECRI Guidelines Trust® and ClinicalTrials.gov. After duplicates were removed, 672 titles and abstracts were screened. After screening, the full text of 381 articles was reviewed. Eighteen studies were included; after multiple reports of the same study were merged, there were 17 included studies. Three hundred sixty-three studies were excluded for the following reasons: wrong study design (282 studies); unspecified dosage form or ROA (48); non-nominated dosage form or ROA (21); language other than English (6); gabapentin only mentioned briefly (4); non-nominated indication (2).

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

Characteristics of included studies

The 17 included studies were published between 2008 and 2020. There were 3 experimental studies, 6 observational studies, and 8 descriptive studies. The 17 studies were conducted in the following countries: the Philippines and US.

A total of 3766 patients participated in the 17 included studies. The number of patients in each study ranged from 1 to 2177.

Outcome measures differed among the included studies and included: pain scores, severity and interference scores, physical examination, pruritus score, and resolution of scalp dysesthesia symptoms.

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

Use of gabapentin

One thousand sixteen patients received gabapentin as a treatment for pain, administered topically in strengths ranging from 2-10%, applied 1-6 times per day. Duration of treatment ranged from 10 days to over 6 months. Fifteen patients received gabapentin as a treatment for pruritus, administered as a topical 6% cream for 14 days. Seven patients received gabapentin as a treatment for scalp dysesthesia, administered topically as a 10% cream two to three times per day. Duration of treatment was not specified.

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

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

In 8 studies, the authors' concluding statement recommended the use of topical gabapentin for the treatment of bortezomib-induced peripheral neuropathy, chronic kidney disease-associated pruritus, chronic pain, cutaneous leiomyomas, trigeminal neuralgia, and vulvodynia.[6,14-20] In 1 study, the authors concluded that compounded pain creams were no better than placebo creams.[21] In 6 studies, the authors' conclusion said that further studies were necessary for the use of topical gabapentin for the treatment of pain and scalp dysesthesia symptoms.[22-27] In 1 study, the authors did not provide a recommendation on the use of topical gabapentin but said that diclofenac-containing topical analgesics may have a more positive effect on pain scores when compared to ketoprofen-containing products.[28] In 1 study, the authors did not provide a concluding statement due to their study being underpowered.[29] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 17 included studies, additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of gabapentin.

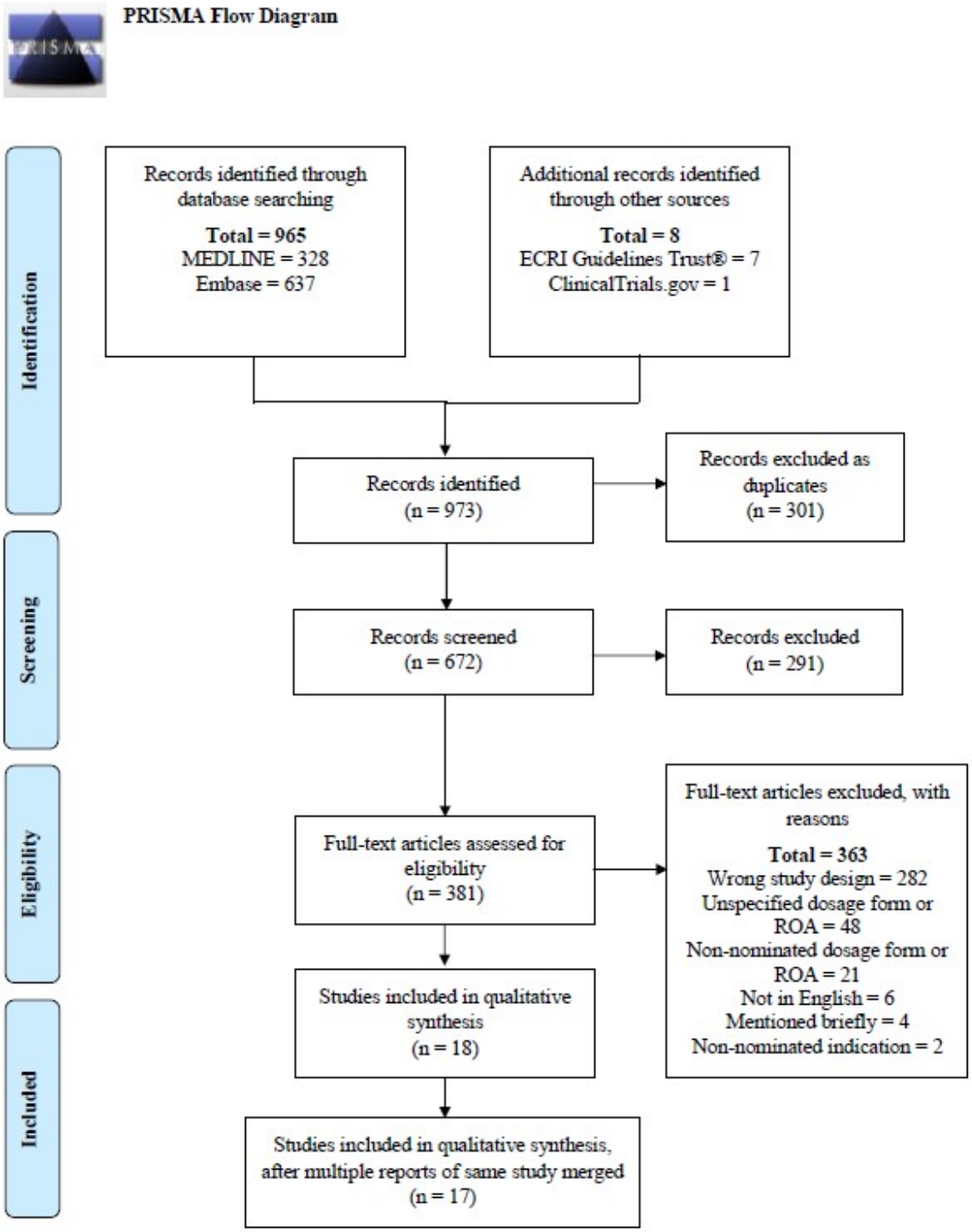
As the "leading cause of years lost to disability worldwide," chronic pain is estimated to effect approximately 31% of the population.[21] Despite this prevalence, there is a lack of reliable treatments for chronic pain, with first-line medications associated with side effects that limit their use.[21] As a result, topical creams have emerged as an alternative to their oral counterparts, in attempt to limit side effects or to overcome a contraindication – such as using nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with chronic kidney disease (CKD).[21,26] 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."[21] While 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.[18,21,26] 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.[21] However, the authors also said that their study was limited by looking at patients who had failed other treatment options, did not include capsaicin (FDA-approved for both neuropathic and nociceptive pain) or amitriptyline (not approved for chronic pain), and the patient population was relatively young and lacking in other pain conditions that topical creams are typically used for (such as knee osteoarthritis and postherpetic neuralgia).[21] 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.[21] 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.[18] 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 Science Engineering and Medicine, the authors concluded that "there is insufficient evidence to determine the effectiveness of gabapentin to treat pain when applied to intact skin."[30]

Gabapentin, with both antiepileptic and analgesic actions, exerts its effect through "inhibiting voltage gated calcium channels to decrease glutamate release and potentiate GABA transmissions."[26] Oral gabapentin is commonly used for patients with neuropathic pain, and is described as first-line therapy for disease states such as diabetic neuropathy, postherpetic neuralgia, central neuropathic pain, and fibromyalgia.[26]

In addition to being used to treat neuropathic pain, gabapentin has also been investigated for the treatment of chronic kidney disease-associated pruritus (CKD-AP), aka uremic pruritus, a complication reported to occur in 30-50% of patients on hemodialysis.[20] One of the included studies commented that CKD-AP is associated with "sleep disturbance, depression, impaired quality of life, and increased risk of mortality."[20] While oral gabapentin has been used to decrease pruritus intensity, there were concerns about increased toxicity in CKD patients due to gabapentin being renally eliminated – this prompted Aquino's 2020 study into topical gabapentin for CKD-AP.[20] In their discussion, they also noted that the topical administration of gabapentin may have also helped avoid some of the drug's typical side effects (fatigue, somnolence, dizziness, nausea, unsteadiness, blurred vision), though systemic absorption is still a possibility with the topical formulation.[20]

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[14-16,19,23-26]	8
Observational[6,17,18,22,27,28]	6
Experimental[20,21,29]	3

Table 4. Number of studies by country

Country	**Number of Studies**
The Philippines[20]	1
US[6,14-19,21-29]	16
	Total US: 16 Total Non-US Countries: 1

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: Pain					
Boardman *et al.*, 2008, US[6]	Retrospective study	51 Patients with generalized or localized vulvodynia (0%, mean 40.2 y ± 16.3 years)	Topical cream containing: • Gabapentin 6% (22) • Gabapentin 4% (10) • Gabapentin 2% (18)	Patient-reported pain scores	"Topical gabapentin seems to be well-tolerated and associated with significant pain relief in women with vulvodynia."
Bonham *et al.*, 2015, US[29] Bonham, 2014, US[31]	Double-blinded, 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[21]	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 (# of patients)	Primary Outcome Measure	Authors' Conclusions
Farid and Mostow, 2019, US[14]	–	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."
Gudin *et al.*, 2016, US[22]	Observational study	158 Out-patients with chronic neurologic or musculoskeletal pain (41%, age not specified)	• "Topical/transdermal analgesic containing compounds such as flurbiprofen 20%, amitriptyline 5%, magnesium chloride 10%, gabapentin 6%, bupivacaine 2%, ketoprofen 5%, diclofenac 20%" (158)	Brief pain inventory (BPI), severity and interference scores	"Overall patient satisfaction with topical/transdermal analgesics was high–they were safe and well-tolerated. Findings were consistent with previous interim analyses (n=631). Further analysis with a larger control group is planned—results may be available for the poster."
Gudin *et al.*, 2016, US[28]	Third interim analysis of an observational study	631 Out-patients with chronic neurologic or musculoskeletal pain (39%, age not specified)	• "Topical/transdermal analgesic containing compounds such as flurbiprofen 20%, amitriptyline 5%, magnesium chloride 10%, gabapentin 6%, bupivacaine 2%, ketoprofen 5%, diclofenac 20%" (158)	BPI, severity and interference scores	"Overall patient satisfaction with topical/transdermal analgesics was high - they were safe and well-tolerated. Findings consistent with previous interim analyses. Diclofenac-containing compounded topical/transdermal analgesics may have a more positive effect on BPI scores than ketoprofen-containing topical/transdermal analgesics."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Haribabu *et al.*, 2013, US[23]	Case report	1 Patient with neuropathic orofacial pain (NOP; 0%, 55 y)	• Gel containing carbamazepine 4%, lidocaine 1%, ketoprofen 4%, and gabapentin 4% in a pluronic lecithin organogel (PLO gel; 1) Gel was applied with a custom-fabricated neurosensory intraoral stent to release the medication directly over the affected area	Patient-reported pain	"The use of topical medication delivered with an intraoral stent as a carrier is not common in the dental community, but we believe it should be encouraged as a mode of treatment in the management of NOP. However, further research needs to be done to study the mechanisms involved, evaluate the effect of various types of compounds and define the optimal doses to be used."
Hohmeier and Almon, 2015, US[24]	Case report	1 Patient with refractory postherpetic neuralgia (PHN) of the head and neck (0%, 78 y)	• Topical cream containing gabapentin 6%, ketoprofen 10%, amitriptyline 2%, and lidocaine 5% (1) • Topical cream containing gabapentin 6%, ketoprofen 10% lidocaine 5%, ketamine 10% and oral mucosal topical analgesic gel with gabapentin 10% (1) Patient switched to new cream due to patient concern of side effects due to experience with amitriptyline. Patient also received intranasal ketamine for breakthrough pain.	Patient-reported pain	"This is the first case report describing the use of a multimodal cream and intranasal ketamine for breakthrough pain in the treatment of PHN. This multimodal cream, intranasal ketamine, or the combination of both should be investigated in larger, randomized, and placebo-controlled trials on the treatment of PHN."
Iqbal *et al.*, 2016, US[15]	Case report	1 Patient presenting with trigeminal neuralgia and history of multiple sclerosis (0%, 51 y)	• Topical cream containing ketamine 10%, gabapentin 10%, imipramine 3%, and bupivacaine 5% (1)	Patient-reported pain	"This case suggests that topical medication could offer an effective, noninvasive, non-opioid therapy for trigeminal neuralgia facial pain."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Prommer, 2009, US[16]	Case	1 Patient with bortezomib-induced peripheral neuropathy (100%, 62 y)	• Gel containing ketamine 5-10%, clonidine 0.5%, and gabapentin 6% (1)	Patient-reported pain	"The patient has been maintained on the ketamine 10% as part of the combination gel. All opioids and agents for neuropathic pain have been stopped. He has been able to return to work and has experienced no adverse effects from the topical combination."
Rizk *et al.*, 2014, US[25]	Case	1 Patient with post-radiation neuropathy and oral mucositis (0%, 76 y)	• A mixture of lidocaine 10 mg/mL, diphenhydramine hydrochloride 0.63 mg/mL, nystatin 25,000 U/mL, and gabapentin 100 mg/mL was prescribed to for the patient to swish-and-swallow (1)	Patient-reported pain, physical examination	"To our knowledge, the current report is unique due to the demonstration of a successful nonconventional topical treatment in combination with standard opioid therapy for radiotherapy-induced oral mucositis and peripheral neuropathic pain. Further applications may be useful in treating other patients with this distressing syndrome."
Safaeian *et al.*, 2016, US[26]	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."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Somberg and Molnar, 2015, US[18]	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[17]	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."
Vadaurri, 2008, US[19]	Case reports	4 In-patients with neuropathic pain (0%, range 54-91 y)	• PLO gabapentin 5% (2) • PLO methadone 0.5% and tetracaine 5% (1) • Methadone 0.5% and tetracaine 5% in Manuka honey (1)	Patient-reported pain	"Topical compounds give practitioners another option in managing patient maladies and, in many instances, compounded topicals have proven as effective, if not more effective, than commercially available products. In some cases, patients have been able to stop oral pain medications or reduce their dose because the topical preparation is so effective. All in all, the topical preparations described in this article have been invaluable to our patients' comfort and an indispensable option for practitioners."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 2: Pruritus					
Aquino *et al.*, 2020, the Philippines[20]	Randomized, double-blind, vehicle-controlled study	30 Patients with chronic kidney disease-associated pruritus on hemodialysis (86.6%, mean 43.8 y ± 12.4)	• Topical gabapentin (15) • Placebo (15)	Visual analog scale pruritus score	"Our results suggest that short-term use of topical gabapentin may significantly decrease CKD-AP [chronic kidney disease-associated pruritus] severity after 2 weeks with no reported acute adverse events."
Indication 3: Scalp dysesthesia					
Thornsberry and English, 2013, US[27]	Retrospective review	15 Patients presenting with scalp dysesthesia (0%, range 38-78 y)	• Topical gabapentin (6) • Oral gabapentin (4) • Topical and oral gabapentin (1) Four patients did not receive gabapentin via any ROA.	Resolution of scalp dysesthesia symptoms such as burning, pruritus, or both	"Four patients reported improvement in symptoms with gabapentin, but the optimal dosage and route of administration need to be studied. Larger, prospective studies are needed to further characterize the pathogenesis of scalp dysesthesia and to determine the most efficacious treatments."

Abbreviations: "–", not mentioned; BPI, brief pain inventory; CKD-AP, chronic kidney disease-associated pruritus; IQR, interquartile range; NOP, neuropathic orofacial pain; PHN, postherpetic neuralgia; PLO, pluronic lecithin organogel; ROA, route of administration.

[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Pain[6,14-19,21-26,28,29]	Apply 4-6 times per day	4%	Gel	Intraoral	8 weeks
	–	10%	Gel	Oral	–
	Apply 1-4 times per day	6-10%	Cream, Gel	Topical	2 weeks – 3 months Mean 164.3 days ± 24.0 Mean 75.5 days ± 22.5 5.4 months ± 4.8 6.4 months ± 5.1
	Apply 0.5-2 mL 2-3 times per day	2-6%	Cream, Gel	Topical	10 days – at least 8 weeks
	Apply 1-2 g to affected area 3-4 times per day	6%	Cream	Topical	3-4 months
	Swish-and-swallow 4 times per day	100 mg/mL	–	Topical	2 months
Scalp dysesthesia[27]	Apply 2-3 times per day	10%	Cream	Topical	–

Abbreviation: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Pruritus[20]	Apply 2 g/day	6%	Cream	Topical	14 days

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Gabapentin 5% / Amantadine hydrochloride 8% / Amitriptyline hydrochloride 2% / Baclofen 4% / Clonidine hydrochloride 0.2% / DMSO 5% / Ketoprofen 10% / Lidocaine hydrochloride monohydrate 5% – topical cream	0
Others found in literature	Gabapentin 6% / Amitriptyline 4% / Baclofen 2% / Bupivacaine 2% / Clonidine 0.2% / Ketamine 10% / Nifedipine 2% – topical cream[17]	1
	Gabapentin 6% / Baclofen 2% / Bupivacaine 1% / Cyclobenzaprine 2% / Diclofenac 5% / Ibuprofen 3% / Pentoxifylline 1% – topical cream[26]	1
	Gabapentin 6% / Amitriptyline 4% / Baclofen 2% / Bupivacaine 2% / Clonidine 0.2% / Ketamine 10% – topical cream[17]	1
	Gabapentin / Baclofen / Bupivacaine / Cyclobenzaprine / Diclofenac / Ketamine – topical cream[14]	1
	Gabapentin 6% / Baclofen 2% / Cyclobenzaprine 2% / Diclofenac 3% / Ketamine 10% / Lidocaine 2% – topical cream[21]	1
	Gabapentin 10% / Baclofen 2% / Clonidine 0.2% / Flurbiprofen 20% / Lidocaine 5% – topical cream[18]	1
	Gabapentin 6% / Amitriptyline 2% / Ketoprofen 10% / Lidocaine 5% – topical cream[24]	1
	Gabapentin 10% / Bupivacaine 5% / Imipramine 3% / Ketamine 10% – topical cream[15]	1
	Gabapentin 6% / Clonidine 0.2% / Ketamine 10% / Lidocaine 2% – topical cream[21]	1
	Gabapentin 4% / Carbamazepine 4% / Ketoprofen 4% / Lidocaine 1% – topical gel[23]	1
	Gabapentin 100 mg/mL / Diphenhydramine hydrochloride 0.63 mg/mL / Lidocaine 10 mg/mL / Nystatin 25,000 U/mL – mouthwash[25]	1
	Gabapentin 6% / Ketamine 10% / Ketoprofen 10% / Lidocaine 5% – topical cream[24]	1
	Gabapentin 6% / Clonidine 0.5% / Ketamine 5-10% – topical gel[16]	1
	Gabapentin 10% / Benzocaine 20% – oral gel[24]	1

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Pain[6,15,17,18,21-24,26,29]	2008-2019	Gabapentin powder was dissolved into ethoxy diglycol, then levigated into PPCA Lipoderm base	Cream	2-6%
		"Compounded in Cetaphil™"	Cream	6%
		"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	6%
		"Compounded topical/transdermal analgesic"	–	6%
		Carbamazepine, lidocaine, ketoprofen, and gabapentin compounded in a pluronic lecithin organogel (PLO gel) and an anhydrous gel base	Gel	4%
		"Compounded combination topical analgesic cream"	Cream	6%
		Gabapentin was compounded with commercially available Orabase® (benzocaine 20% gel)	Gel	10%
		"Topical compounding cream"	Cream	10%
		"The topical compound was prepared by one of two established compounding pharmacies"	Cream	6%
		"Compounded topical creams"	Cream	10%
		"Compounded topical cream"	Cream	6%
Scalp dysesthesia[27]	2013	Gabapentin powder with a lipophilic liposomic base, with propylene glycol as the wetting agent	Cream	10%

Abbreviation: "–", not mentioned.

Table 10. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Pruritus[20]	Contents of gabapentin capsules (6 g) were dissolved in water and compounded into a permeation cream (100 g). Major components were propylene glycol and polyethylene glycol; other ingredients included purified water, petrolatum, sorbitol, cetearyl alcohol, ceteareth-20, simethicone, glyceryl stearate, sorbic acid, and butylated hydroxytoluene.	Cream	6%

Results of interviews

One hundred eighty-four SMEs were contacted for interviews; 64 agreed to be interviewed, and 120 declined or failed to respond to the interview request. Seven SMEs discussed gabapentin. Amongst these 7 SMEs, there were 4 medical doctors, 1 nurse practitioner, and 2 doctors of podiatric medicine. The SMEs specialized and/or were board-certified in infectious diseases, obstetrics and gynecology, oncology, pain management, and podiatry, 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, project in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

Gabapentin is commonly as a first option to treat neuropathic pain; however, there were differing opinions regarding the use of topical gabapentin with most SMEs utilizing the oral version. One SME stated that they utilize topical pain products and that the differing pathologies of pain a patient presents with will determine the formulation. The SME stated that "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." 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). However, they are never first-line options and are only used if the patient asks for a product they do not have to take by mouth or if the patient has tried topical lidocaine or Voltaren® (diclofenac) gel with no relief. Another SME had never used topical gabapentin but stated that "it'd be great if it works because neuropathic pain is a pretty specific area so topical would work really well there." Similarly, another stated that "if there would be a true topical option, that would be great because most of my patients cannot tolerate the oral version" citing improper titration leading to subtherapeutic doses and side effects.

Three SMEs commented on the use of gabapentin for the treatment of vulvodynia. Vulvodynia is a clinical diagnosis with a variety of different forms; "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 ones who eventually will undergo surgery might go months or years before receiving the appropriate surgery. As a result, they may use compounded products to treat the problem in the meantime. While some products contain lidocaine, an SME cautioned that "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 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."

Often, products for vulvodynia will contain gabapentin or similar agents, varying from 3-5% concentrations, either alone or in combination with amitriptyline; "amitriptyline and the gabapentin are really used for people who pain is a major component, especially when it's unprovoked pain. But may be also used when it's provoked. And both of them 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 what they... Maybe 10 if you're using different concentrations with each." These agents

are applied once or twice daily but there are not a lot of studies determining the correct combination or benefits. Another SME commented that gabapentin can be compounded in concentrations up to 10%, but they predominately use gabapentin 6% in combination with amitriptyline and baclofen. This combination treats pain using different mechanisms. One SME stated that they prefer oral gabapentin when treating vulvodynia but have on occasion used gabapentin 6% in Aquaphor. Some products might come with additional estrogen in the form of either estradiol or estriol; "estriol is a little bit less potent than estradiol. But it's better tolerated." Sometimes they add estrogen or testosterone as a solo product, or they combine it 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." When asked about the efficacy for topical products, one SME said that "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, and there is debate on whether the studies that have been completed are treating 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 has encountered challenges with patients being able to afford the compounded products since "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 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." Another SME said that "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 gabapentin nomination].

Gabapentin 5% / amantadine hydrochloride 8% / amitriptyline hydrochloride 2% / baclofen 4% / clonidine hydrochloride 0.2% / ketoprofen 10% / lidocaine hydrochloride monohydrate 5% / 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. This product will be compounded without the following inactive ingredients silicon dioxide, methylparaben, titanium dioxide, talc, lactose, mineral oil, magnesium stearate, propylene glycol, hypromellose, and propylparaben, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants and their hazardous concerns include allergen, human endocrine disruptor, human immune toxicant or allergen, classified as expected to be toxic or harmful, and possible human carcinogen. Gabapentin is added to mediate pain, amitriptyline for its ability to inhibit both serotonin and noradrenaline reuptake, baclofen to treat spasticity, clonidine for its analgesic effects, 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 and because 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 obtain 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 one 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 five-minute gown and glove. If we don't have somebody in the IV [intravenous] room, if you're doing 797 right, it's five minutes. It's four minutes to tube it. It's three 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 presser 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 in 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, while they do not obtain a lot of products from outsourcing facilities, stated that "when we do purchase from 503B's, 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 COVID-19 pandemic has also impacted the operations of hospitals with 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 clean room 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 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 mid-size 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 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 with one-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 utilized. However, the products

utilized 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 nine 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 continued 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 Hospital Pharmacists] and the FDA allows." 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 for bulk... especially for the pediatric patient population." However, another participant from a children's hospital stated that the need for a preservative free option has never been a reason why they have obtained a product from an outsourcing facility. 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 clean room 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 is 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 being available. 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 are doing the non-sterile 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 non-sterile 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 [United States Pharmacopeia] <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 noting that it "is a challenge for anybody who has the 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 whom 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 an 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 three 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 12-24 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 2,400, either one, compounder. Then we send it up to 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 "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 "Traditionally, we've found 503B's 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 503B's where we've had agreements for certain products to take it off our plate, and then low 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 (DEA) 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

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

Forty-three people responded to the prequestionnaire; refer to Table 15 for respondent characteristics. Amongst 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, where respondents were allowed to select multiple reasons) obtained drug products from outsourcing facilities due to a need for ready-to-use products and 20 respondents (14%) obtained drug products from outsourcing facilities due to backorders (refer to Table 16).

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

Gabapentin was not included on the prequestionnaire (refer to Table 18).

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which gabapentin prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded gabapentin

No respondents to survey distributed via professional medical associations

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

No respondents to survey distributed via professional medical associations

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=38)**
< 50	4
50-99	3
100-199	1
200-299	3
300-399	5
400-599	3
> 600	18

[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]	6

[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

Gabapentin was nominated for inclusion on the 503B Bulks List as a topical and vaginal cream to treat vulvodynia and pain. Gabapentin is not available in the nominated dosage form and ROA in any of the national registries searched.

From the literature review gabapentin is commonly used to treat pain in concentrations from 2-10%. While there were no studies included that discussed the nominated combination, there were studies found in which gabapentin was used as a compounded product and in combination with additional APIs. From the interviews, there were differing opinions regarding the use of topical gabapentin for neuropathic pain. Most SMEs had never utilized the topical formulation but stated that if it was effective, it may be a useful treatment option for neuropathic pain. For vulvodynia, three SMEs had used gabapentin, however, there is minimal literature available regarding the effectiveness.

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

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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 August 19, 2020
- Date last searched: August 20, 2020
- Limits: Humans (search hedge); English language
- Number of results: 328

1	gabapentin/	3784
2	gabatin$.tw.	0
3	gabapentin$.tw.	6523
4	or/1-3	7160
5	administration, topical/	38441
6	administration, cutaneous/	22073
7	administration, intravaginal/	4853
8	administration, mucosal/	260
9	skin absorption/	11691
10	topical$.tw.	105549
11	epicutaneous$.tw.	2011
12	transdermal$.tw.	14609
13	((cutaneous$ or dermal$ or skin) adj3 (absorb$ or absorpt$ or appl$)).tw.	12277
14	vagina$.tw.	110922
15	muco?sal$.tw.	120322
16	transmuco?sal$.tw.	1894
17	emulsions/	17960
18	exp gels/	51988
19	liniments/	123
20	ointments/	12792

21	skin cream/	1033
22	"vaginal creams, foams, and jellies"/	1276
23	emulsion?.tw.	33168
24	liniment?.tw.	145
25	ointment?.tw.	11856
26	salve?.tw.	341
27	paste?.tw.	12495
28	unguent$.tw.	113
29	lotion?.tw.	2307
30	cream?.tw.	18954
31	or/5-30	497550
32	and/4,31	381
33	exp animals/ not humans/	4726918
34	32 not 33	360
35	limit 34 to english language	328

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: August 20, 2020
- Limits: Humans (search hedge); English language
- Number of results: 637

1	‘gabapentin'/mj	4364
2	‘gabatin*':ti,ab,tn	6
3	‘gabapentin*':ti,ab,tn	10580
4	#1 OR #2 OR #3	11104
5	‘topical drug administration'/de	82612
6	‘cutaneous drug administration'/de	664
7	‘transdermal drug administration'/de	9063
8	‘intravaginal drug administration'/de	6502
9	‘mucosal drug administration'/de	441
10	‘skin absorption'/de	8048
11	‘topical treatment'/de	13018
12	‘topical*':ti,ab	149506
13	‘epicutaneous*':ti,ab	3415
14	‘transdermal*':ti,ab	21384
15	‘vagina*':ti,ab	173387
16	‘muco$sal*':ti,ab	172268
17	‘transmuco$sal*':ti,ab	2534
18	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp* OR appl*)):ti,ab	17952
19	‘cream'/de	9438
20	‘gel'/exp	77008
21	‘liniment'/de	251
22	‘lotion'/de	2860

23	‘ointment'/de	17915
24	‘paste'/de	2520
25	‘salve'/de	166
26	‘cream$':ti,ab	29668
27	‘emulsion$':ti,ab	45101
28	‘liniment$':ti,ab	234
29	‘lotion$':ti,ab	4004
30	‘ointment$':ti,ab	21592
31	‘paste$':ti,ab	14985
32	‘salve$':ti,ab	476
33	‘unguent*':ti,ab	240
34	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33	738554
35	#4 AND #34	713
36	[animals]/lim NOT [humans]/lim	6076761
37	#35 NOT #36	681
38	#35 NOT #36 AND [english]/lim	637

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 gabapentin to your patients?
    - Yes
    - No
3. Do you prescribe or administer gabapentin by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Topical product
    - Vaginal product
    - None of the above
4. I prescribe or administer gabapentin for the following conditions or diseases: (check all that apply)
    - Pain
    - Vulvodynia
    - Other (please explain) _____
5. I prescribe or administer compounded gabapentin in combination with other active pharmaceutical ingredients.
    - Yes
    - No
6. I use compounded gabapentin 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 gabapentin
    - Other (please explain) _____
7. Do you stock non-patient-specific compounded gabapentin at your practice?
    - Yes
    - No
    - I'm not sure
8. I obtain compounded gabapentin 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 specialtiy(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.