Summary Report

Ibuprofen

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Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
NSAID	Nonsteroidal anti-inflammatory drug
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 ibuprofen (UNII code: WK2XYI10QM), 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 ibuprofen 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 ibuprofen 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 ibuprofen 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

Ibuprofen was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA), Sincerus, and Triangle Compounding Pharmacy, Inc. Ibuprofen was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Ibuprofen was nominated for fever, pain, inflammation, and fungal infections via a topical gel, cream, ointment, solution, suspension, oral capsule and suspension, and rectal suppository. The strength will vary based on the prescribers' request and the dosage form compounded.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of ibuprofen.[6-17]

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

- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patient need for dosage form or strength, including greater concentration, that is not available commercially.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Need for accuracy; individual finished products have variance in actual API and use of a finished product has the potential to introduce unacceptable inaccuracies into the compounded medication.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of ibuprofen 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 ibuprofen; name variations of ibuprofen 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 ibuprofen. 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 three concepts: ibuprofen; topical or rectal administration; and therapeutic use, or substances nominated for use in combination with (refer to Appendix 1 for full search strategies). Due to the availability of FDA-approved and OTC oral ibuprofen products, the nominated oral dosage forms were not included in the systematic literature review. Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on March 26, 2020. The reference lists of relevant systematic reviews and meta-analyses were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on March 26, 2020 for clinical practice guidelines that recommended the use of ibuprofen and provided sufficient information on dosing and administration.

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

Study selection

Studies in which ibuprofen 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 ibuprofen was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which ibuprofen 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 ibuprofen; setting; total number of patients; number of patients who received ibuprofen; patient population; indication for use of ibuprofen; dosage form and strength; dose; ROA; frequency and duration of therapy; use of ibuprofen in a combination product; use and formulation of ibuprofen in a compounded product; use of ibuprofen 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 ibuprofen was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify the following medical specialties that would potentially use ibuprofen: pain management, and primary care and internal medicine. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

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

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

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

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

CURRENT AND HISTORIC USE

Results of background information

- Ibuprofen is available as an FDA-approved product in the nominated dosage form and ROA.
- Ibuprofen is available as OTC oral capsules, suspensions, and tablets in the US.
- There is a current United States Pharmacopeia (USP) monograph for ibuprofen.
- Ibuprofen is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Hong Kong, Ireland, New Zealand, Saudi Arabia, and UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Ibuprofen	100 mg/5 mL	Suspension	Oral	Prescription	3/25/1998

[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[c]	Approval Date[b]
Ibuprofen	200-400 mg	Capsule	–	Abu Dhabi	Active	–
	200 mg			New Zealand	Pharmacy-only	11/26/2009
	100-400 mg		Oral	Australia	Schedule 2, Schedule 3	1/15/2001
				UK	Pharmacy	9/17/1997
	200-300 mg			Hong Kong	Pharmacy-only	3/19/1984
	100-200 mg			Ireland	Pharmacy-only	3/8/2002

	300 mg			Saudi Arabia	Prescription	–
	100 mg/5ml	Suspension		Abu Dhabi	Active	–
				Hong Kong	Pharmacy-only	4/27/1999
				Namibia	–	11/25/1983
	20-40 mg/ml			Australia	Schedule 2	2/3/1998
				Ireland	Pharmacy-only	3/2/1981
				New Zealand	Prescription, pharmacy-only	6/9/1995
				UK	Pharmacy	7/2/2009
	60-150 mg	Suppository	–	Ireland	Pharmacy-only	9/12/2008
	50 mg/g	Cream		Abu Dhabi	Active	–
	5%	Gel	Topical	Australia	–	8/20/2001
				Ireland	Pharmacy-only	9/19/1995
	5-10%			UK	Prescription, pharmacy-only	1/14/1991

Abbreviation: "– ", not mentioned.

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

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

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

Results of literature review

Study selection

Database searches yielded 1398 references; 6 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 1002 titles and abstracts were screened. After screening, the full text of 106 articles was reviewed. Finally, 11 studies were included. Ninety-five studies were excluded for the following reasons: wrong study design (58 studies); used in FDA-approved form (15); ibuprofen used as brand or proprietary product (7); ibuprofen only mentioned briefly (6); wrong dosage form or ROA (4); unable to obtain (3); wrong indication (1); language other than English (1).

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

Characteristics of included studies

The 11 included studies were published between 1996 and 2019. There were 11 experimental studies, 0 observational studies, 0 descriptive studies, and 0 clinical practice guidelines. The 11 studies were conducted in the following countries: Denmark, Finland, Italy, Turkey, UK, and US.

A total of 1114 patients participated in the 11 included studies. The number of patients in each study ranged from 10 to 138.

Outcome measures differed among the included studies and included: visual analog scale for pain, need for additional pain medication, daily diary of symptoms, use of ice, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), 5-point pain scale, duration of morning stiffness, handgrip strength, adverse events, pain threshold, and time to pain relief.

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

Use of ibuprofen

Five hundred fifty-five patients received ibuprofen as an experimental treatment for pain, administered rectally in doses ranging from 10-15 mg/kg to 1000 mg/day, or application of 5 cm to 16 inches of a topical dosage form for a total dose of 1.5-6 g/day. Duration of treatment ranged from once to 20 days for rectal administration, and once to 24 months for topical administration.

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

Ibuprofen was not used as a compounded product, nor was it used in a combination product.

In 7 studies, the authors' concluding statement recommended the use of topical ibuprofen for the treatment of pain in acute ankle sprain and knee osteoarthritis.[14,16,18-22] In 3 studies, the authors' concluded that the use of topical ibuprofen was not recommended or further studies were necessary for the treatment of muscle soreness from exercise.[23-25] In 1 study, the authors concluded that there was no difference between topical ibuprofen and its comparator.[26] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 11 included studies, a few studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of ibuprofen.

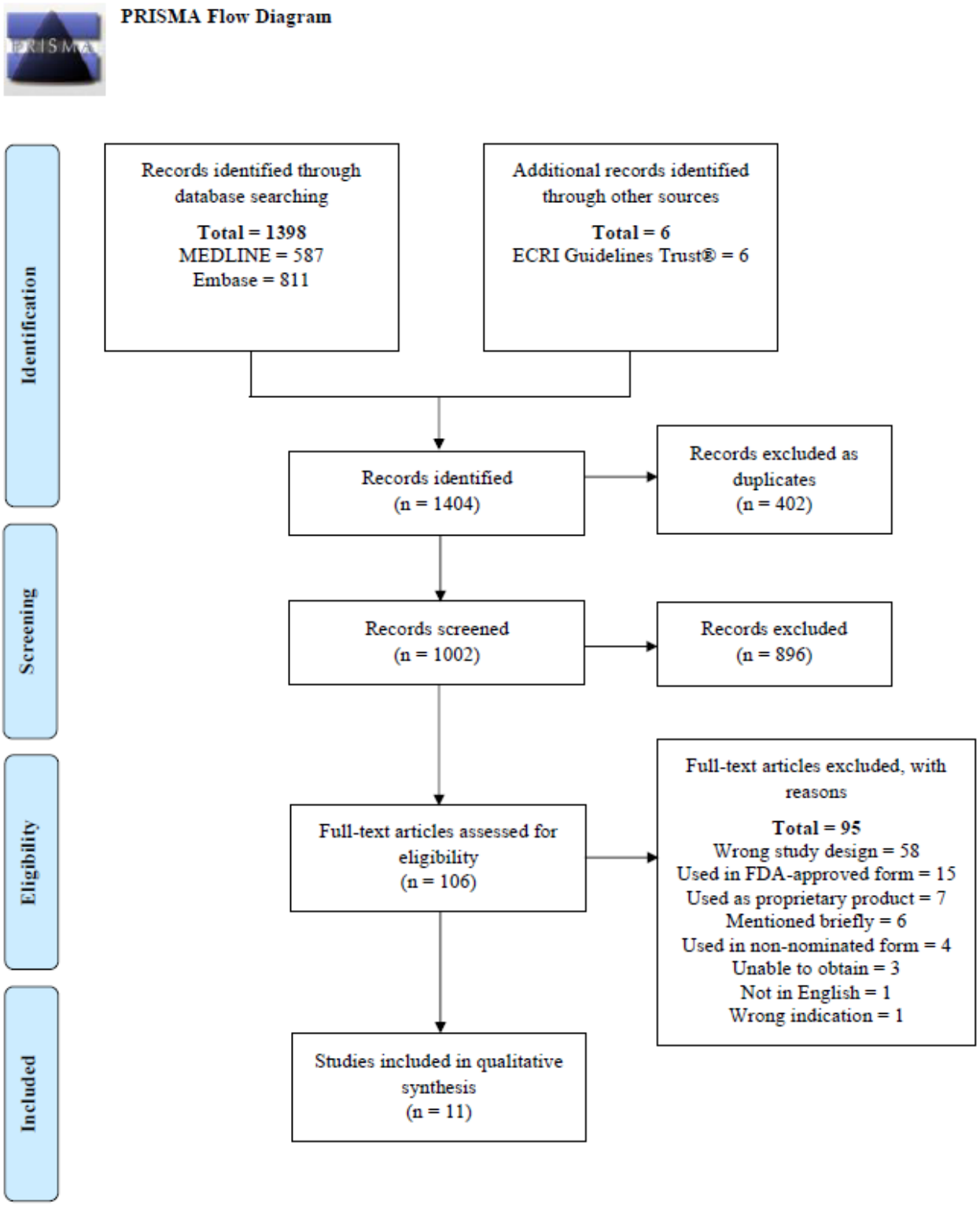
Ibuprofen is used for various conditions involving pain and inflammation. Oral dosage forms are commonly used, but they are "associated with gastric, renovascular and respiratory adverse effects, which are a particular risk for older people."[14] Topical and rectal dosage forms of ibuprofen have been investigated to determine if administration of these formulations will result in the same benefits of oral ibuprofen without the unwanted systemic side effects.[22]

A 2004 meta-analysis by Mason et al studied the effect of topical nonsteroidal anti-inflammatory drugs (NSAIDs) for acute pain.[27] Five out of 26 included studies used topical ibuprofen in a total of 365 patients. In the included studies, topical ibuprofen was more effective than placebo. Efficacy estimates were made for 5 drugs that were studied in at least trials; the result for ketoprofen was significantly better than for ibuprofen, felbinac, piroxicam and indomethacin. The authors concluded that topical NSAIDs were safe and effective for the treatment of acute pain for 1 week but made no specific recommendations about ibuprofen.

The topical or oral ibuprofen for chronic knee pain in older people (TOIB) study, commissioned by the Health Technology Assessment Programme in Great Britain, explored the effect of advice to preferentially use oral or topical ibuprofen on knee pain and disability through a randomized control trial and patient preference study.[14] The study found that advice to use either oral or topical NSAIDs had an equivalent effect on knee pain, which the authors noted suggested that "the two treatment strategies are either equally effective or equally ineffective."[14] However, oral NSAIDs "appear to produce more minor adverse effects than topical NSAIDs," a finding which the authors suggested supported the recommendation to advice older people to use topical NSAIDs rather than oral.[14]

A 2014 Osteoarthritis Research Society International guideline recommended topical NSAIDs for knee-only osteoarthritis as they are safer and better tolerated than oral NSAIDs.[28] This guideline cited a 2011 Cochrane review in which "topical NSAIDs were associated with lower risk of GI [gastrointestinal] adverse events but higher risk of dermatological events compared with oral NSAIDs".[28]

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	0
Experimental[14,16,18-26]	11
Observational	0

Table 4. Number of studies by country

Country	**Number of Studies**
Denmark[21]	1
Finland[25]	1
Italy[20]	1
Turkey[18,19,24]	3
UK[14,16,22,26]	4
US[23]	1
	Total US: 1 Total Non-US Countries: 10

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: Pain, soreness					
Balcioglu *et al.*, 2017, Turkey[24]	Randomized single-blind controlled trial	163 Patients diagnosed with soft tissue trauma Overall average (34%, 52.4 y ± 14.7) Ibuprofen (mean 51.4 y ± 14.7)	• 1% Diclofenac gel (56) • 5% Diclofenac gel (50) • 5% Ibuprofen gel (57)	Pain on visual analog scale, at admission and days 3 and 5; need for additional oral pain medication (paracetamol)	"The gel containing 5% diclofenac was evaluated to be more effective than the other gels in this study and its adverse event profile was found to be similar since no adverse event was observed."
Campbell *et al.*, 1994, UK[16]	Randomized, double-blind placebo controlled	51 Patients with soft-tissue ankle injury Ibuprofen (65%, mean 26.4 y ± 2.1) Placebo (64%, mean 34.3 y ± 3)	• Ibuprofen cream (26) • Placebo cream (25)	Daily diary of symptoms until recovered, which had simple tick boxes about function, use of ice, tubigrip, and paracetamol; visual analog scales for pain at rest, standing and walking	"This study shows that the use of topical ibuprofen is associated with a statistically significant reduction in pain over the first 48 hours of treatment following an acute ankle sprain. The amount of pain reduction is of the order of 10% more with ibuprofen cream than with placebo…Although oral NSAID [nonsteroidal anti-inflammatory drug] therapy is likely to confer a similar benefit this is at the risk of potentially serious side-effects."
Coskun *et al.*, 2018, Turkey[18]	Single-blinded, randomized, comparative	61 Patients diagnosed with clinical knee osteoarthritis (OA) Gel phonophoresis (10%, median 55 y (range 43-86)) Cream phonophoresis (13%, median 60 y (range 38-76))	• Ibuprofen gel + continuous ultrasound (30) • Ibuprofen cream + continuous ultrasound (31)	Visual analog scale for pain, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) before and after ten sessions	"Ibuprofen phonophoresis is effective in reducing pain, stiffness, and functional limitation. Phonophoresis with the gel-based preparation of ibuprofen is associated with higher clinical improvement than cream ibuprofen phonophoresis."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Hyldahl *et al.*, 2010, US[23]	Double-blind, randomized crossover study	106 Adult subjects unaccustomed to gym exercise (39%, men mean 32.8 y ± 13.4, women mean 37.3 y ± 15.1)	• Ibuprofen, then placebo (53) • Placebo, then ibuprofen (53)	Pain/soreness at baseline and at 36, 37, 38, 39, 40, 41, 42, 48, 60, 66, 72, 84, 90, 96, 108 hours after exercise	Topical ibuprofen gel did not significantly reduce soreness after an unaccustomed exercise session; there was no difference in the effects of gel by age or sex.
Kozanoglu *et al.*, 2003, Turkey[19]	Prospective, randomized controlled trial	60 Patients who fulfilled American College of Radiology criteria for OA of the knee Ibuprofen (17%, mean 60.3 y ± 9.2) Continuous ultrasound (13%, mean 59.4 y ± 8.9)	• Ibuprofen cream + ultrasound (30) • Acoustic gel with no pharmacologically active substances + ultrasound (30)	30% improvement in total WOMAC scores at end of therapy, compared with baseline	"In this randomized controlled study, marked improvements in clinical parameters were obtained with ibuprofen PH [phonophoresis] or therapeutic US [ultrasound] in patients with knee OA, and neither modality was found to be superior to the other."
Rizzi *et al.*, 1979, Italy[20]	Double-blind, randomized, parallel-group comparative study	30 In-patients on a general surgical unit for reasons unrelated to their concomitant OA Ibuprofen (47%, mean 58.5 y) Flurbiprofen (47%, mean 59.5 y)	• Ibuprofen suppository (15) • Flurbiprofen suppository (15)	Patient's assessment of pain, on 5-point scale; duration of morning stiffness; right- and left-hand grip strength; proctoscopic assessment of anorectal mucosa; record of hemoglobin, proteinuria, serum glucose, transaminases, bilirubin, alkaline phosphatase, uric acid, urea, and cholesterol All assessments carried out at day 0, day 10, and day 20	"This study indicates that both flurbiprofen and ibuprofen suppositories are potent analgesics in osteoarthrosis, with a very low incidence of anorectal intolerance."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Smith *et al.*, 1996, UK[26]	Double-blind study	10 Healthy volunteers, subjected to pinprick and venipuncture Sex, age not provided	Study 1 (10)* • Ibuprofen cream • EMLA cream • Placebo cream Study 2 (10)* • Ibuprofen cream • EMLA cream *Participants acted as their own controls	Study 1: skin reaction (redness, blanching, edema), sensitivity to pinprick, on visual analog scale Study 2: pain on insertion of 20-gauge cannula, measured on visual analog scale	"In summary, there are no differences in VAS scores during pinprick when topical ibuprofen, EMLA and placebo creams are compared at 15 and 60 min. EMLA for 60 min is associated with significantly lower VAS pain scores during venous cannulation than ibuprofen cream applied for 60 min. In addition there are no significant differences in skin reactions, technical ease of cannulation or cannula-associated thrombophlebitis between EMLA and ibuprofen creams. We conclude therefore, that ibuprofen cream applied in a thick layer under an occlusive plastic dressing does not offer any clinical advantage over EMLA cream for venous cannulation."
Svensson *et al.*, 1997, Denmark[21]	Randomized, placebo-controlled, double-blind study	10 Healthy volunteers (100%, mean 25.8 y ± 0.5)	• Placebo gel and placebo tablets (10) • Ibuprofen gel and placebo tablet (10) • Placebo gel and ibuprofen tablet (10)	Pressure pain threshold, pain tolerance threshold, maximum voluntary occlusal force at end of exercise, 1 hour after, and day 1, day 2 and day 3 after exercise	"Pressure pain threshold [PPT] at the masseter muscle was the only outcome measure that was affected by treatments. Administration of topical NSAID as compared to systemic NSAID was associated with significantly higher PPT, indicating a minor advantage."
Underwood *et al.*, 2008, UK[14]	Randomized controlled trial; patient preference study	282 Patients with knee pain for at least 1 month, experienced for more than 3 months of the preceding year Oral (44%, mean 62.8 y ± 8.3) Topical (49%, mean 62.6 y ± 8.5)	• Oral ibuprofen (144) • Topical ibuprofen (138)	WOMAC, adverse events at baseline, and 3, 6, 12, and 24 months after allocation	"The outcome data from participants in our study were very similar in terms of both efficacy and adverse effects, regardless of treatment group. We conclude that where the use of an NSAID is considered appropriate, the best strategy for primary care practitioners treating older people with chronic knee pain would be to suggest treatment with topical agents in preference to oral NSAIDs, unless the patient has a strong desire to use oral treatment and is not at high risk of adverse effects from oral NSAID use."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Viitanen *et al.*, 2003, Finland[25]	Randomized, double blind, placebo-controlled study	159 Children undergoing adenoidectomy with or without myringotomy Acetaminophen: sex not provided; mean 2.7 y (range 1-6.4) Ibuprofen: mean 3.2 y (range 1-6.9) Combination: 3.2 y (range 1-6.9) Placebo: 2.6 y (range 1-6.3)	• Acetaminophen (40) • Ibuprofen (41) • Combination (40) • Placebo (38)	Parent questionnaire evaluating pain, use of rescue ibuprofen, vomiting, tiredness, sleep of child for 24 hours after anesthesia	"We conclude that prophylactically administered rectal acetaminophen combined with ibuprofen does not improve analgesia after adenoidectomy in the immediate postoperative period compared with either drug alone but does decrease the need for analgesia at home. Ibuprofen results in lesser sedation and faster discharge than when acetaminophen is used."
Wade *et al.*, 2019, UK[22]	Randomized, single-blind, parallel-group, single-dose study	182 Patients ages 16-75 y with acute soft tissue injury (60%, mean 36.18 y ± 12.09)	• Ibuprofen/levomenthol gel (59) • Ibuprofen gel (61) • Diclofenac gel (61)	Time to pain relief, defined as reduction of 2 points on 11-point numeric rating scale	"The addition of levomenthol to ibuprofen gel was associated with improved analgesic performance when compared with a gel containing only ibuprofen. While all three gels were associated with effective pain relief, our results indicate that ibuprofen/ levomenthol gel and diclofenac gel had a shorter median time to significant pain relief compared with ibuprofen gel, although statistically significant differences were not demonstrated. Based on median global pain relief 2 hours after application, ibuprofen gel containing levomenthol produced pain relief that was superior to that of standard ibuprofen gel and similar to that of diclofenac gel. Only ibuprofen/levomenthol gel provided prolonged cooling for up to 2 hours after gel application."

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Pain, soreness[23]	–	10%	Gel	Topical	Once

Abbreviations: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Pain, soreness, stiffness[14,16,18-22,24-26]	1000 mg/day 10-15 mg/kg	500 mg	Suppository	Rectal	Once - 20 days
	5 cm (175 mg)/session 16 inch/day	5%	Cream	Topical	10 sessions 15 min – 2 weeks
	1.5- 6 g/day 5 cm/session	5%	Gel		Once – 24 months 10 sessions

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Ibuprofen 1% / Miconazole nitrate 2% / Tea tree oil 1%	0
	Ibuprofen 2% / Cimetidine 5% / Salicylic acid 17%	0
	Ibuprofen 2% / Fluconazole 4% / Itraconazole 1% / Terbinafine HCl 4%	0
	Ibuprofen 2% / Ciclopirox 2% / Itraconazole 1% / Terbinafine HCl 4% / Urea 10%	0
	Ibuprofen 2% / Cimetidine 10% / Deoxy-d-glucose 0.2% / Lidocaine 5% / Salicylic acid 15%	0
	Ibuprofen 2% / Clobetasol propionate 0.05% / Mupirocin 5% / Salicylic acid 5% / Urea 20%	0

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Twelve SMEs discussed ibuprofen. Amongst these 12 SMEs, there were 4 medical doctors, 5 dentists, 2 pharmacists, and 1 nurse practitioner. The SMEs specialized and/or were board-certified in dermatology, maxillofacial surgery, oncology and hematology, palliative care, pharmacotherapy, and primary care and family medicine, working in academic medical practice, consulting, formerly academic medical practice, private practice/clinic, and retired. The SMEs had been in practice for 5 to 40 years.

Several of the SMEs utilized oral ibuprofen for pain management, relying on it as a "workhorse medication." The SMEs stated that the accessibility and limited adverse effects make it popular amongst practitioners, although they acknowledged that prolonged use could lead to kidney issues. Although the combination of ibuprofen and Tylenol® (acetaminophen) was not nominated, several SMEs mentioned its use. According to the SMEs specializing in dentistry most dental pain can be relieved by OTC ibuprofen products. After dental procedures, SMEs prescribed 800-1000 mg of Tylenol® (acetaminophen) to be taken in combination with 600-650 mg of ibuprofen orally every 6 hours. Research shows this combination "is more beneficial for post-op pain from tooth extractions than opioid medications."

Pain tolerability is different based on individuals. One SME said it has nothing to do with age, weight, or stature, saying "some people can tolerate pain and some people can't." As such, patients need different products that address different degrees of pain. This can lead to practitioners prescribing opioids for pain, with the associated risk of addiction. One SME said it is important to understand the pain pathways in the body and how they work so you can treat them effectively. An SME who works with patients with substance abuse issues has heard "that's not going to touch [the pain]" when these patients are offered ibuprofen.

Cancer pain is another possible use for ibuprofen. An SME noted that while ibuprofen is used in oncology, it has to be carefully considered "because it can affect clotting and cause GI [gastrointestinal] distress." An SME said "if [ibuprofen] could be used topically, that would make sense and it would be great."

Several SMEs were enthusiastic about topical ibuprofen, saying they would "love an ibuprofen that was a topical gel or an ointment." Certain patients, such as those with kidney insufficiency, obesity, diabetes, hypertension or arthritis, cannot take oral NSAIDs, and the SMEs did not want to give those patients opioids long-term. Regarding ibuprofen as a gel, one SME said, "I wouldn't say that it doesn't get absorbed into your blood and into your kidneys, but not nearly to the degree where you take it by mouth." One SME provided the example of Voltaren® (diclofenac), an NSAID currently available as a gel, saying that if ibuprofen was a gel, "that would be great." However, another SME stated that Voltaren® (diclofenac) is available so they do not have a need for topical ibuprofen. The SMEs did acknowledge that they were not aware of any studies "that tell us it is a lot safer" in topical form.

Regarding the combinations, one SME commented on the nominated topical combination of clobetasol / ibuprofen / mupirocin / salicylic acid / urea, saying "Of the things you have shown me, that is the most intriguing." This SME said that mupirocin is used as an antibiotic, salicylic acid is used like aspirin, and urea is used to help with absorption. They have used urea for patients with thick skin when they want to reduce flakiness. The combination of ibuprofen and cimetidine surprised another SME, since cimetidine is an older medication which has been largely replaced by Prilosec® (omeprazole). The SME thought a combination of ibuprofen and Prilosec® might avoid any potential drug interactions from cimetidine with ibuprofen.

Another SME did not currently use ibuprofen with patients, and 2 SMEs did not see a use for topical ibuprofen, although one commented that knowing how a topical form might compare to what is already available could impact their decision. Only one SME commented on all of the nominated formulations, saying "I would love to see those," because they do not currently have access to these diverse options.

Results of survey

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

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which ibuprofen prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded ibuprofen

No respondents to survey distributed via professional medical associations

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

No respondents to survey distributed via professional medical associations

CONCLUSION

Ibuprofen was nominated for inclusion on the 503B Bulks List as topical gel, cream, ointment, solution, suspension, oral capsule and suspension, and rectal suppository to treat fever, pain, inflammation, and fungal infections. Ibuprofen is available in the nominated dosage forms and ROA in Abu Dhabi, Australia, Hong Kong, Ireland, New Zealand, Saudi Arabia, UK and US.

From the literature review and interviews conducted, ibuprofen has been used for pain, soreness, and stiffness. Eleven studies were included from the literature review: 9 in which topical ibuprofen gel or cream was used to treat pain and soreness associated with soft tissue injury or osteoarthritis, and 2 in which rectal ibuprofen was administered for osteoarthritis or postoperative pain. In 9 studies, the authors found that topical or rectal ibuprofen reduced pain and soreness.[14,16,18-22,25,26] In 1 study, topical ibuprofen did not significantly reduce soreness after exercise.[23] In another study, 5% diclofenac gel was superior to 5% ibuprofen gel in patients with soft tissue trauma.[24] No significant adverse events were reported with the use of topical or rectal ibuprofen. The topical or oral ibuprofen for chronic knee pain in older people (TOIB) study, commissioned by the Health Technology Assessment Programme in Great Britain, found that advice to use either oral or topical NSAIDs had an equivalent effect on knee pain, but oral NSAIDs "appear to produce more minor adverse effects than topical NSAIDs", a finding which the authors suggested supported the recommendation to advise older people to use topical NSAIDs rather than oral.[14] Several SMEs expressed an interest in having access to topical ibuprofen formulations, remarking that such formulations would be useful for patients who cannot tolerate, or have underlying conditions that prevent the administration of, oral NSAIDs. One SME did not see a need for topical ibuprofen formulations, given the OTC availability of a topical diclofenac product; this SME was not sure how topical ibuprofen would compare with topical diclofenac.

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 March 25, 2020
- Date last searched: March 26, 2020
- Limits: Humans (search hedge); English language
- Number of results: 587

1	ibuprofen/	8716
2	ibuprofen$.tw.	13176
3	ibuprophen$.tw.	29
4	or/1-3	14683
5	administration, topical/	38082
6	administration, cutaneous/	21806
7	administration, rectal/	2515
8	topical$.tw.	103092
9	transdermal$.tw.	14282
10	rectal$.tw.	86566
11	exp gels/	50786
12	suspensions/	7698
13	liniments/	122
14	ointments/	12747
15	skin cream/	983
16	suppositories/	3917
17	gel?.tw.	304172
18	suspension?.tw.	106950
19	liniment?.tw.	143
20	ointment?.tw.	11663

21	salve?.tw.	338
22	paste?.tw.	12164
23	unguent$.tw.	111
24	lotion?.tw.	2265
25	cream?.tw.	18520
26	suppositor$.tw.	4365
27	or/5-26	681820
28	exp fever/	42744
29	exp inflammation/	331228
30	analgesia/	19738
31	exp pain/	389954
32	pain management/	32988
33	exp mycoses/	125391
34	drug therapy/	30395
35	dt.fs.	2189838
36	ad.fs.	1396544
37	tu.fs.	2195842
38	pc.fs.	1267073
39	fever$.tw.	166763
40	pyrexi$.tw.	4751
41	antipyret$.tw.	5065
42	inflamm$.tw.	903040
43	analgesi$.tw.	120865
44	pain$.tw.	676467
45	fung$.tw.	204503
46	antifung$.tw.	48566

47	mycos$.tw.	16371
48	mycot$.tw.	19725
49	dermatomyco$.tw.	1237
50	ciclopirox/	397
51	cimetidine/	9221
52	clobetasol/	1367
53	deoxyglucose/	11138
54	fluconazole/	7680
55	itraconazole/	5706
56	lidocaine/	24241
57	miconazole/	2013
58	mupirocin/	1218
59	salicylic acid/	6424
60	tea tree oil/	421
61	terbinafine/	1787
62	urea/	43050
63	c#clopirox$.tw.	548
64	clobetasol$.tw.	1085
65	de?oxyglucos$.tw.	9483
66	de?oxy d glucos$.tw.	7371
67	de?oxy dextro glucos$.tw.	0
68	de?oxy dextroglucos$.tw.	0
69	fluconazol$.tw.	12020
70	itraconazol$.tw.	8688
71	onikonazol$.tw.	0
72	orikonazol$.tw.	0

73	lidocain$.tw.	21405
74	lignocain$.tw.	2889
75	mi#onazol$.tw.	2690
76	mupirocin$.tw.	1781
77	pseudomonic acid$.tw.	89
78	salicylic acid$.tw.	12301
79	((melaleuca or tea or ti) adj2 oil).tw.	699
80	terbinafin$.tw.	2498
81	carbamid$.tw.	1466
82	carbonamid$.tw.	16
83	carbonylamid$.tw.	9
84	karbamid$.tw.	0
85	urea.tw.	81296
86	uree.tw.	101
87	or/28-86	6323788
88	and/4,27,87	832
89	exp animals/ not humans/	4682817
90	88 not 89	640
91	limit 90 to english language	587

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 26, 2020
- Limits: Humans (search hedge); English language
- Number of results: 811

1	ibuprofen'/mj	13319
2	ibuprofen*':ti,ab,tn	18869
3	ibuprophen*':ti,ab,tn	60
4	#1 OR #2 OR #3	23394
5	rectal drug administration'/de	8656
6	topical drug administration'/exp	110821
7	topical*':ti,ab	146387
8	transdermal*':ti,ab	20833
9	rectal*':ti,ab	137230
10	cream'/de	9189
11	gel'/exp	73601
12	liniment'/de	248
13	lotion'/de	2806
14	ointment'/exp	18380
15	paste'/de	2490
16	salve'/de	165
17	suppository'/de	6013
18	suspension'/exp	108726
19	cream$':ti,ab	29040
20	liniment$':ti,ab	231
21	lotion$':ti,ab	3941
22	ointment$':ti,ab	21290

23	paste$':ti,ab	14645
24	salve$':ti,ab	469
25	suppositor*':ti,ab	7075
26	suspension$':ti,ab	142522
27	unguent*':ti,ab	239
28	#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	709506
29	fever'/de	249461
30	inflammation'/exp	3698323
31	analgesia'/de	126264
32	pain'/exp	1363803
33	mycosis'/exp	210970
34	topical treatment'/de	12424
35	antifungal therapy'/de	4148
36	drug dose':lnk	622258
37	drug administration':lnk	1722607
38	drug therapy':lnk	3852451
39	prevention':lnk	1161499
40	fever*':ti,ab	255568
41	pyrexi*':ti,ab	10180
42	antipyret*':ti,ab	8191
43	inflamm*':ti,ab	1335370
44	analgesi*':ti,ab	178065
45	pain*':ti,ab	1037337
46	fung*':ti,ab	253968
47	antifung*':ti,ab	68116
48	mycos*':ti,ab	23799

49	mycot*':ti,ab	24690
50	dermatomyco*':ti,ab	2135
51	ciclopirox'/de	1093
52	clobetasol'/de	2760
53	deoxyglucose'/de	11774
54	fluconazole'/de	42680
55	itraconazole'/de	29392
56	lidocaine'/de	74951
57	miconazole'/de	10182
58	pseudomonic acid'/de	6914
59	salicylic acid'/de	25940
60	tea tree oil'/de	1228
61	terbinafine'/de	7573
62	urea'/de	82472
63	ciclopirox*':ti,ab,tn	798
64	cyclopirox*':ti,ab,tn	34
65	clobetasol*':ti,ab,tn	1807
66	de$oxyglucos*':ti,ab,tn	11403
67	de$oxy d glucos*':ti,ab,tn	8609
68	de$oxy dextro glucos*':ti,ab,tn	0
69	de$oxy dextroglucos*':ti,ab,tn	0
70	fluconazol*':ti,ab,tn	17172
71	itraconazol*':ti,ab,tn	12093
72	onikonazol*':ti,ab,tn	0
73	orikonazol*':ti,ab,tn	0
74	lidocain*':ti,ab,tn	29905

75	lignocain*':ti,ab,tn	4014
76	miconazol*':ti,ab,tn	3483
77	myconazol*':ti,ab,tn	31
78	mupirocin*':ti,ab,tn	2544
79	pseudomonic acid*':ti,ab,tn	128
80	salicylic acid*':ti,ab,tn	14812
81	((melaleuca OR tea OR ti) NEAR/2 oil):ti,ab	911
82	terbinafin*':ti,ab,tn	3574
83	carbamid*':ti,ab,tn	1617
84	carbonamid*':ti,ab,tn	30
85	carbonylamid*':ti,ab,tn	6
86	karbamid*':ti,ab,tn	2
87	urea':ti,ab,tn	110724
88	uree':ti,ab,tn	152
89	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88	9565140
90	#4 AND #28 AND #89	1239
91	[animals]/lim NOT [humans]/lim	6009256
92	#90 NOT #91	984
93	#90 NOT #91 AND [english]/lim	811

Appendix 2. Survey instrument for professional medical associations

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

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

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

Thank you,

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

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

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

1. How familiar are you with the following terms?

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

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

   - o Yes
   - o No

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

   - o Oral capsule
   - o Oral suspension
   - o Rectal suppository
   - o Topical cream
   - o Topical gel
   - o Topical ointment
   - o Topical solution
   - o Topical suspension
   - o None of the above

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

   - o Fever
   - o Fungal infections
   - o Inflammation
   - o Pain
   - o Other (please explain) _____

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

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

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

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

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

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

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

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

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

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

Appendix 3. Survey distribution to professional associations

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

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

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

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