Summary Report

Guaifenesin

Prepared for:

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

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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FMS	Fibromyalgia syndrome
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 guaifenesin (UNII code: 495W7451VQ), 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 guaifenesin 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 guaifenesin 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 guaifenesin 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 NOMINATION

Guaifenesin was nominated for inclusion on the 503B Bulks List by Triangle Compounding Pharmacy, Inc.

Guaifenesin was nominated to treat cough and muscle pain/spasms via oral capsules of various strengths between 200-600 mg and topical dosage forms (gels, creams, ointments) of strengths between 1-10%.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of guaifenesin.[6-11]

The reason provided for nomination to the 503B Bulks List was that there would be fewer side effects with the nominated preparations. The FDA-approved capsules contain inactive ingredients and excipients, which are either not appropriate for topical use or patients have intolerances or allergies to them.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of guaifenesin 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 guaifenesin; name variations of guaifenesin 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 guaifenesin. 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: guaifenesin, and topical administration or therapeutic use for myofascial pain (refer to Appendix 1 for full search strategies). Oral administration was not included in the literature review due to the availability of FDA-approved products for this ROA. 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 April 9, 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 April 9, 2020 for clinical practice guidelines that recommended the use of guaifenesin 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 guaifenesin 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 guaifenesin 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 guaifenesin 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 guaifenesin; setting; total number of patients; number of patients who received guaifenesin; patient population; indication for use of guaifenesin; dosage form and strength; dose; ROA; frequency and duration of therapy; use of guaifenesin in a combination product; use and formulation of guaifenesin in a compounded product;

use of guaifenesin 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 guaifenesin was used in a clinical setting. The systematic literature review and indications from the nomination were reviewed to identify the following medical specialties that would potentially use guaifenesin: orthopedics and pain management. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of guaifenesin 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

- Guaifenesin is available as an FDA-approved product in the nominated dosage form and ROA.
- Guaifenesin is available as an OTC oral tablet in the US.
- There is a current United States Pharmacopeia (USP) monograph for guaifenesin.
- Guaifenesin is available in the nominated dosage form and ROA in Abu Dhabi, Ireland, Namibia, Saudi Arabia, and UK.

Table 1. Currently approved products – US

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Guaifenesin	600-1200 mg	Tablet	Oral	OTC	07/12/2002

Abbreviation: "– ", not mentioned.

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

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Guaifenesin	10-20 mg/mL	Syrup	Oral	Abu Dhabi	Active	–
				Ireland	Pharmacy-only[c]	07/27/1998
				Namibia	–	08/25/1987
				UK	Pharmacy	10/11/1989
	600 mg	Tablet	Oral	Abu Dhabi	Active	–
				Saudi Arabia	Prescription	–

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 220 references; 1 additional reference was identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 186 titles and abstracts were screened. After screening, the full text of 17 articles was reviewed. Finally, 0 studies were included. Seventeen studies were excluded for the following reasons: wrong study design (13 studies); wrong dosage form or ROA (2); language other than English (1); guaifenesin used as brand or proprietary product (1).

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

Characteristics of included studies

No studies were included from the literature review.

Use of guaifenesin

No studies were included from the literature review.

Pharmacology and historical use

Eight studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of guaifenesin.

Guaifenesin, also known as guaiacol glyceryl ether, was evaluated in a 1963 study as a centrally active muscle relaxant.[12] The author utilized intravenous guaifenesin in an attempt to avoid the respiratory impairment associated with other skeletal muscle relaxants in combination with general anesthesia.[12] The author concluded that guaifenesin was best used as an adjuvant to other relaxants and anesthetics, and "not as a muscle relaxant unaided by at least surgical anaesthesia."[12]

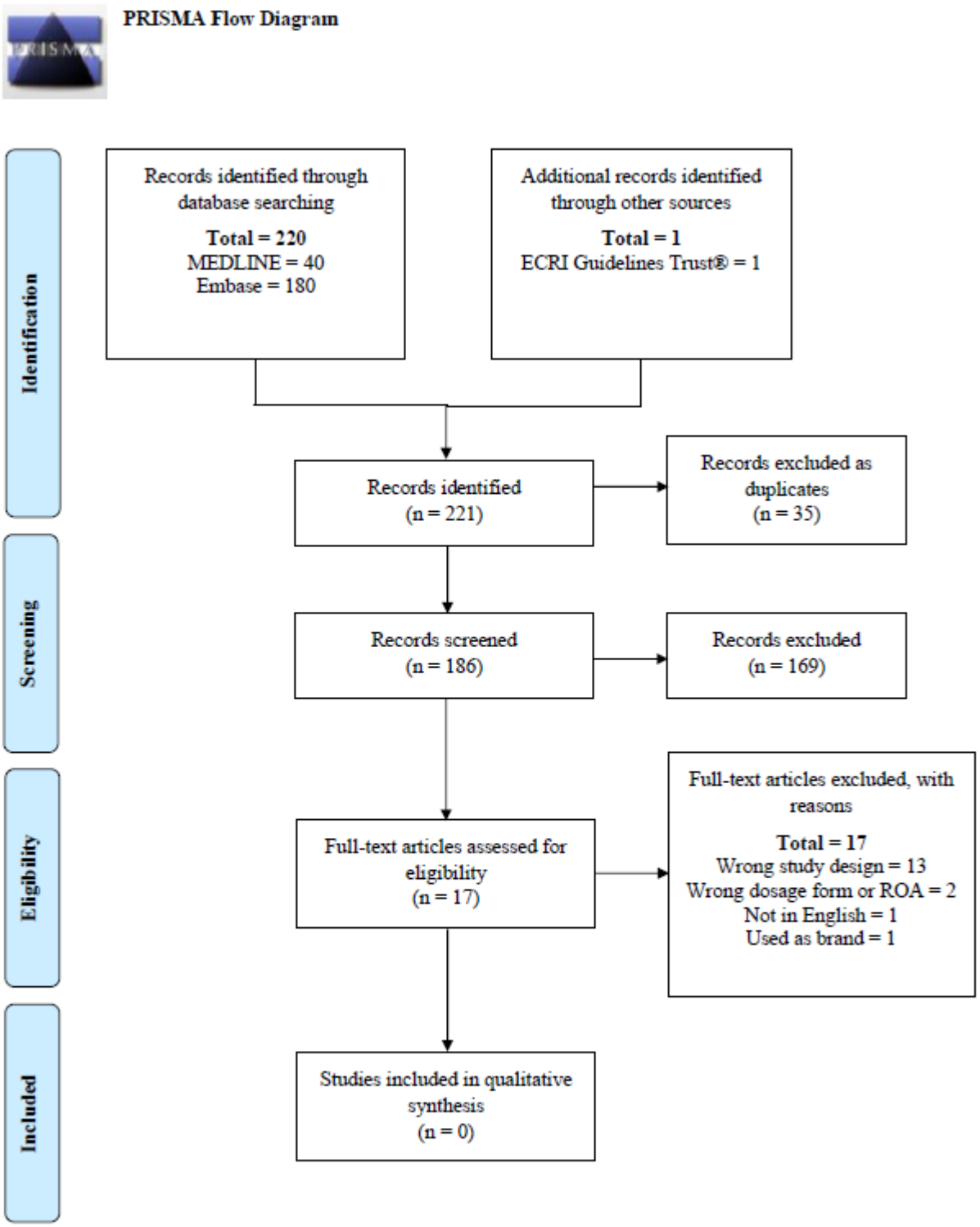
Oral guaifenesin has been considered for the treatment of fibromyalgia syndrome (FMS) to decrease phosphate in patients.[13-17] Guaifenesin was first used for FMS in a study by St. Amand and Marek; it was taken with a protocol that involved the elimination of salicylate use and management of dietary carbohydrates.[17] However, a double-blind, placebo-controlled study of guaifenesin 600 mg twice daily, concluded that oral guaifenesin was no more effective than placebo in treating FMS.[14-16] Despite the lack of controlled trials displaying the effectiveness of guaifenesin in patients with FMS, another review commented that many patients reported improvement when guaifenesin was administered in the protocol laid out by St. Amand and Marek.[17]

Oral guaifenesin was the subject of a phase II proof-of-concept, multicenter, placebo-controlled, repeat-dose, parallel-group study to look at efficacy and safety for upper back, neck, and shoulder pain.[8] The authors noted that there was potential for OTC dosing of guaifenesin (1200 mg twice daily) "to provide symptomatic relief of upper back musculoskeletal pain and spams." However, they needed a larger, more adequately powered study to confirm these results.[8]

While there were no studies included on the topical use of guaifenesin, the formulas for several topical preparations were published in the *International Journal of Pharmaceutical Compounding* and *U.S. Pharm*. Indications for use of these topical preparations were not provided. These formulations included a cream with ketoprofen 10%, guaifenesin 10%, amitriptyline hydrochloride 3%, and capsaicin 0.075% in a Lipopen Ultra Cream Base; a penetrating gel containing cyclobenzaprine

hydrochloride 1%, dextromethorphan hydrobromide 10%, guaifenesin 10%, and indomethacin 20%; and a rapidly penetrating gel containing dextromethorphan hydrobromide 10% and guaifenesin 10%.[18-20] In addition, the formula for a trigger point gel was found, used for the treatment of mild to moderate degrees of pain; this gel contained ketoprofen, guaifenesin, capsaicin, lidocaine hydrochloride, and amitriptyline hydrochloride in a Pluronic F-127 20% Gel.[21]

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

No studies included

Table 4. Number of studies by country

No studies included

Table 5. Summary of included studies

No studies included

Table 6. Dosage by indication – US

No studies included

Table 7. Dosage by indication – non-US countries

No studies included

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No studies included

Table 10. Compounded products – non-US countries

No studies included

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. Six SMEs discussed guaifenesin. Amongst these 6 SMEs, there were 1 medical doctor, 2 pharmacists, 1 nurse practitioner, 1 physician assistant, and 1 dentist. The SMEs specialized and/or were board-certified in anesthesiology, oral and maxillofacial surgery, oncology/hematology, pain management, palliative care, and pharmacotherapy, working in academia, academic medical centers, and private practice/clinics. The SMEs had been in practice for 6 to 34 years.

The SMEs were all familiar with guaifenesin as a cough medication. One SME said that they use it all of the time for cough, usually in combination with something, such as an antihistamine to help dry patients up. The most effective and popular regimen is to use guaifenesin in combination with Hycodan® (hydrocodone bitartrate and homatropine methylbromide) or codeine.

However, the SMEs were less familiar with guaifenesin for muscle pain and spasms. One SME said that it would not have occurred to them to use guaifenesin for muscle pain and spasms. Another SME said they had not seen guaifenesin used for muscle pain but had seen another OTC cough product, dextromethorphan, used for pain.

Only one SME was aware of guaifenesin being used as a topical cream but did not provide any further information regarding its use. Other SMEs said that they do not see a need for a topical product since the oral version is commercially available.

One SME said that guaifenesin does not work well for cough or muscle spasms and "all you are doing is making it in a more expensive formulation and it is a fancier form of stupid."

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 guaifenesin prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded guaifenesin

No respondents to survey distributed via professional medical associations

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

No respondents to survey distributed via professional medical associations

CONCLUSION

Guaifenesin was nominated for inclusion on the 503B Bulks List as oral capsules and topical dosage forms (gels, creams, ointments) for the treatment of cough and muscle pain/spasms. Oral guaifenesin is approved in Abu Dhabi, Ireland, Namibia, Saudi Arabia, UK, and US.

From the literature review and interviews conducted, guaifenesin was first evaluated as a centrally active muscle relaxant in an attempt to avoid respiratory depression shown with other muscle relaxants. Currently oral guaifenesin is familiar to many practitioners as an oral OTC cough product. It has also been used for the treatment of FMS as part of a protocol by St. Amand and Marek; however, there is a lack of controlled trials displaying effectiveness. Oral guaifenesin has also been looked at for muscle pain, but the study was not adequately powered to confirm the authors' results. No studies were found regarding the use of guaifenesin as a topical product, but formulas for topical preparations with unknown indications were found in the review of the literature. The SMEs did not see a need for a topical product with the oral version commercially available and were generally unfamiliar with using guaifenesin for muscle spasms. One SME said that guaifenesin was fairly ineffective for both cough and muscle spasms.

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

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20. Dextromethorphan hydrobromide 10% and guaifenesin 10% rapidly penetrating gel. *Int J Pharm Compd.* 2009;13(1):66.

21. Trigger point gel. *Int J Pharm Compd.* 2010;14(1):75.

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 April 8, 2020
- Date last searched: April 9, 2020
- Limits: Humans (search hedge); English language
- Number of results: 40

1	guaifenesin/	576
2	guai?fenesin$.tw.	361
3	guai?phenesin$.tw.	51
4	guayanesin$.tw.	0
5	quaifenesin$.tw.	0
6	(glycer$ adj2 guai?c$).tw.	160
7	glycer#?guai?col$.tw.	6
8	or/1-7	818
9	administration, topical/	38127
10	administration, cutaneous/	21846
11	topical$.tw.	103324
12	transcutaneous$.tw.	14188
13	cutaneous$.tw.	149061
14	transdermal$.tw.	14323
15	derm$.tw.	238153
16	emulsions/	17716
17	exp gels/	50893
18	liniments/	123
19	ointments/	12746
20	skin cream/	986

21	emulsion?.tw.	32305
22	gel?.tw.	304821
23	liniment?.tw.	143
24	ointment?.tw.	11689
25	salve?.tw.	339
26	paste?.tw.	12202
27	unguent$.tw.	113
28	lotion?.tw.	2267
29	cream?.tw.	18571
30	myalgia/	1642
31	fibromyalgia/	8325
32	exp spasm/	9708
33	myalg$.tw.	9451
34	myodyn$.tw.	86
35	fibromyalg$.tw.	10106
36	fibromyosit$.tw.	22
37	fibrofascitis.tw.	1
38	fibrosit$.tw.	536
39	myospas$.tw.	34
40	((myofascia$ or muscl$) adj2 (pain$ or relax$ or sore$ or spasm$ or tender$)).tw.	26694
41	or/9-40	922190
42	and/8,41	86
43	exp animals/ not humans/	4688807
44	42 not 43	72
45	limit 44 to english language	40

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: April 9, 2020
- Limits: Humans (search hedge); English language
- Number of results: 180

1	guaifenesin'/de	2186
2	guai$fenesin*':ti,ab,tn	498
3	guai$phenesin*':ti,ab,tn	93
4	guayanesin*':ti,ab,tn	0
5	quaifenesin*':ti,ab,tn	1
6	(glycer* NEAR/2 guai$c*):ti,ab,tn	225
7	glyceroguai$col*':ti,ab,tn	8
8	glycerylguai$col*':ti,ab,tn	5
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	2326
10	topical drug administration'/de	81599
11	cutaneous drug administration'/de	624
12	transdermal drug administration'/de	8892
13	topical treatment'/de	12463
14	topical*':ti,ab	146576
15	cutaneous*':ti,ab	213926
16	transcutaneous*':ti,ab	18987
17	transdermal*':ti,ab	20865
18	derm*':ti,ab	372977
19	cream'/de	9201
20	gel'/exp	73818
21	liniment'/de	248
22	lotion'/de	2810

23	ointment'/exp	18390
24	paste'/de	2491
25	salve'/de	165
26	emulsion'/exp	44345
27	cream$':ti,ab	29072
28	emulsion$':ti,ab	44043
29	lotion$':ti,ab	3945
30	ointment$':ti,ab	21309
31	paste$':ti,ab	14666
32	salve$':ti,ab	470
33	unguent*':ti,ab	239
34	liniment*':ti,ab	239
35	gel$':ti,ab	357866
36	myalgia'/exp	106084
37	muscle spasm'/exp	89754
38	myalg*':ti,ab	15811
39	myodyn*':ti,ab	148
40	fibromyalg*':ti,ab	16285
41	fibromyosit*':ti,ab	49
42	fibrofascitis':ti,ab	1
43	fibrosit*':ti,ab	793
44	myospas*':ti,ab	64
45	((myofascia* OR muscl*) NEAR/2 (pain* OR relax* OR sore* OR spasm* OR tender*)):ti,ab	39414
46	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45	1429758
47	#9 AND #46	276

48	[animals]/lim NOT [humans]/lim	6013762
49	#47 NOT #48	248
50	#47 NOT #48 AND [english]/lim	180

Appendix 2. Survey instrument

Welcome. We want to understand your clinical use of compounded guaifenesin. 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 guaifenesin to your patients?

    - o Yes
    - o No

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

    - o Topical gel
    - o Topical cream
    - o Topical ointment
    - o None of the above

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

    - o Muscle pain
    - o Muscle spasms
    - o Other (please explain) _____

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

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

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

7. I obtain compounded guaifenesin 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.