Summary Report

Pentoxifylline

Prepared for:

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
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
TNF	Tumor necrosis factor
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) to evaluate the use of pentoxifylline (UNII code: SD6QCT3TSU), 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 pentoxifylline 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 pentoxifylline 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 pentoxifylline 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

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

Pentoxifylline was nominated for use as an anti-inflammatory agent in dermatologic conditions in various topical dosage forms, including but not limited to cream, gel, ointment, solution, and suspension. The strength is based on prescriber's request with a therapeutic dose of 0.5%

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of pentoxifylline.[6-9]

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
- Patients 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
- Individual finished products have a considerable variance in the actual amount of active product ingredient and the 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 pentoxifylline 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 pentoxifylline; name variations of pentoxifylline 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 pentoxifylline. 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: pentoxifylline and, topical administration or substances nominated for use in combination with (refer to Appendix 1 for full search strategies). 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 pentoxifylline 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 pentoxifylline 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 pentoxifylline 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 pentoxifylline 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 pentoxifylline; setting; total number of patients; number of patients who received pentoxifylline; patient population; indication for use of pentoxifylline; dosage form and strength; dose; ROA; frequency and duration of therapy; use of pentoxifylline in a combination product; use and formulation of pentoxifylline in a compounded product; use of pentoxifylline 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 pentoxifylline 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 pentoxifylline: dermatology. 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 pentoxifylline 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

- Pentoxifylline is not available as an FDA-approved product in the nominated dosage form and ROA.
- Pentoxifylline is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for pentoxifylline.
- Pentoxifylline is not available in the nominated dosage form and ROA in any of the foreign 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 872 references; 1 additional reference was identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 713 titles and abstracts were screened. After screening, the full text of 190 articles was reviewed. Finally, 2 studies were included. One hundred eighty-eight studies were excluded for the following reasons: wrong study design (167 studies); used in FDA-approved form (11); wrong dosage form or ROA (4); pentoxifylline not used clinically (2); duplicate study (1); unable to obtain (1); pentoxifylline used as brand or proprietary product (1); wrong indication (1).

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

Characteristics of included studies

The 2 included studies were published in 2012 and 2018.[10,11] There was 1 experimental study, 0 observational studies, 1 descriptive study, and 0 clinical practice guidelines. The 2 studies were conducted in the following countries: Iran and US.

A total of 123 patients participated in the 2 included studies. The number of patients in each study ranged from 1 to 122.

The outcome measure in the experimental study was change in pressure ulcer characteristics.

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

Use of pentoxifylline

One patient received pentoxifylline as a treatment for lipodermatosclerosis. Sixty patients received pentoxifylline as an experimental treatment for pressure ulcer, administered topically twice daily.

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

Pentoxifylline was used as a compounded product but was not used in a combination product (refer to Table 10).

In 1 study, the authors' conclusion stated that pentoxifylline significantly improved pressure ulcers and more studies are needed to evaluate the role of pentoxifylline in the prevention of pressure ulcers. Refer to Table 5 for summary of authors' conclusions.

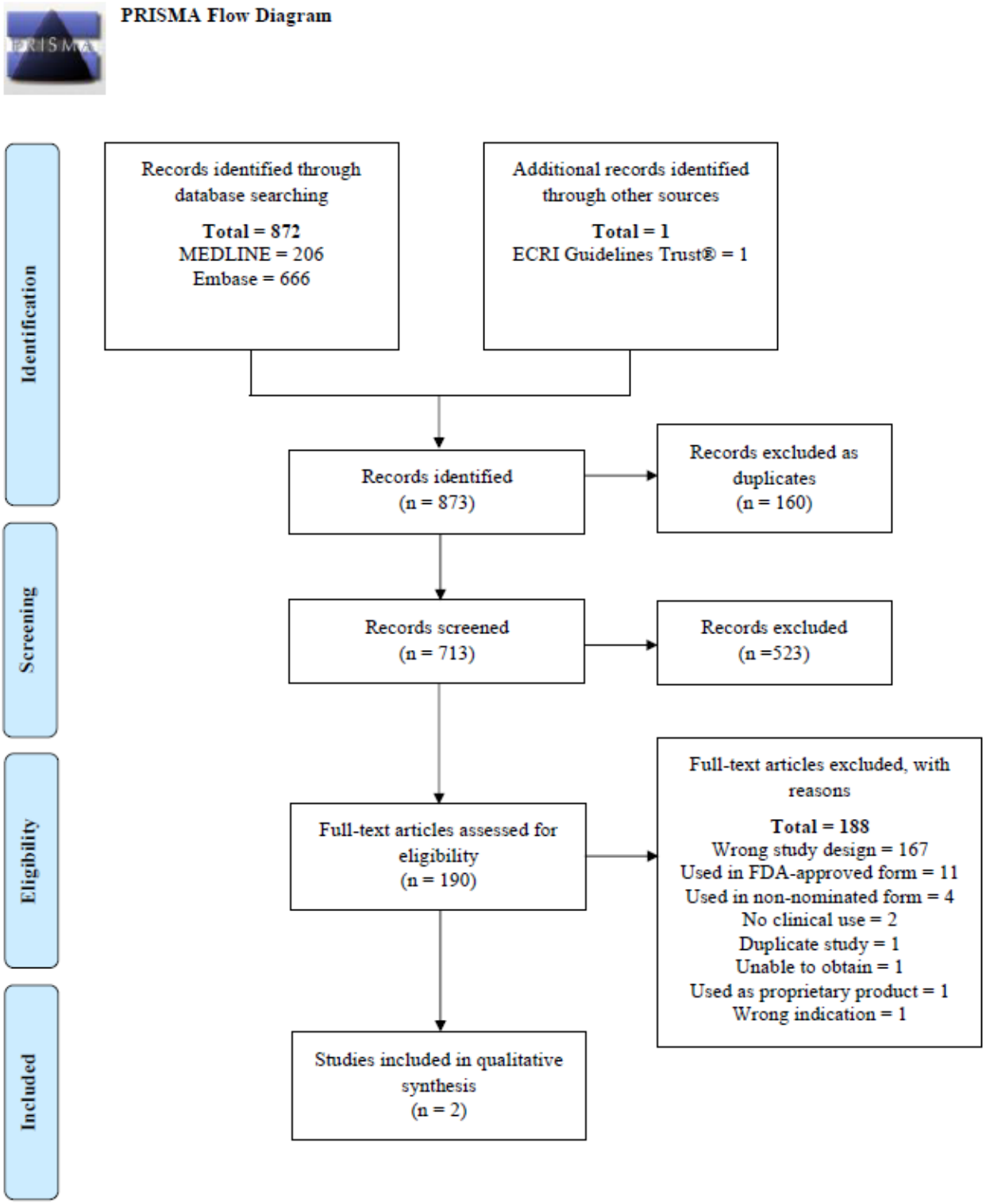
Pharmacology and historical use

In addition to the 2 included studies, 3 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of pentoxifylline.

Pentoxifylline is a methylxanthine derivative, first approved for the treatment of intermittent claudication.[11,12] However, several of its other properties make pentoxifylline a potential agent for wound healing.[11] Pentoxifylline can improve blood flow by increasing erythrocyte and leukocyte elasticity, preventing platelet aggregation, and inducing vasodilation by modulating immunologic activity to produce cytokines.[13] Pentoxifylline also has anti-inflammatory and antioxidant properties.[13] Topical pentoxifylline has been shown to be absorbed percutaneously, and have analgesic, anti-inflammatory, and anti-ischemic effects, as well as improve tissue survival following frostbite.[11]

Pentoxifylline also suppresses the production of tumor necrosis factor (TNF)-alpha and counteracts its activity, which would make it a potential treatment option for allergic contact dermatitis.[12] However, in a 1998 blinded placebo-controlled study by Brehler et al, topical 6% pentoxifylline cream was not able to suppress or prevent contact allergy reactions, leading the authors to conclude that it "should no longer be regarded as a potential candidate for the treatment of allergic contact dermatitis".[12] Another placebo-controlled study by Saricaoglu et al tested the effect of 5%, 10%, and 15% topical pentoxifylline gel for patients with nickel sensitivity, with varying results.[14] Only 1 out of 22 patients showed suppression of allergic reaction with all 3 concentrations, and 1 patient had suppression only with the highest concentration (15%).[14] The results suggested that while the overall effect of pentoxifylline was statistically insignificant, trials at higher concentrations may be warranted.

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[10]	1
Observational	0
Experimental[11]	1

Table 4. Number of studies by country

Country	**Number of Studies**
Iran[11]	1
US[10]	1
	Total US: 1 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: Lipodermatosclerosis (LDS)					
Chernyavsky *et al.*, 2012, US[10]	Case report	44-year-old female with lipodermatosclerosis (LDS)	Pentoxifylline	Improvement in symptoms of leg pain, edema, and erythema	"Treatment of LDS includes compression stockings, leg elevation, using anabolic steroids such as stanazolol, pentoxifyllin and topical capsaicin."
Indication 2: Pressure ulcer					
Najafi *et al.*, 2018, Iran[11]	Randomized, double-blind, placebo controlled clinical trial	122 patients with category I or II pressure ulcers hospitalized for hemodynamic or respiratory support in ICU Pentoxifylline group (55%, mean 52.45) Placebo group (48%, mean 55.90)	• Pentoxifylline (60) • Placebo (62)	Any change in pressure ulcer characteristics (category and size)	"Compared with the placebo, PTX [pentoxifylline] 5% ointment significantly improved category and size of PU [pressure ulcer] in these patients. Antithrombotic, fibrinolytic, anti-inflammatory, immunomodulatory and antioxidant properties of PTX may be attributed to this positive effect. Evaluating the role of PTX in the prevention of PU may be considered in future studies."

[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Lipodermatosclerosis[10]	–	–	–	–	–

Abbreviation: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Pressure ulcer[11]	–	5%	Ointment	Topical	14 days

Abbreviation: "–", not mentioned.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Pentoxifylline 0.5% / Betamethasone dipropionate 0.05% / Minoxidil 5% / Niacinamide 2%	0
	Pentoxifylline 0.5% / Tranilast 1% / Triamcinolone acetonide 0.1%	0
	Pentoxifylline 0.5% / Tranilast 1% / Triamcinolone acetonide 0.1% / Zinc oxide 5%	0

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Pressure ulcer[11]	For ointment base, eucerin (79 g) and solid paraffin (8 g) were mixed and melted in a water bath until it yielded a homogenous mixture. Following this, pentoxifylline powder (5 g) was added to water (8 g). When the ointment base reached a temperature of 37C, pentoxifylline solution was gradually added to produce a final ointment of 5% pentoxifylline.	Ointment	5%

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. One SME discussed pentoxifylline. This SME was a medical doctor who was board-certified in dermatology, working as a consultant, formerly in an academic medical center. The SME had been in practice for 40 years.

The SME stated that in dermatology, only 8 disease states (including acne, eczema, and psoriasis) are big enough to warrant drug development. For other disease states, dermatologists need to come up with a rational approach for treatment.

One condition treated by dermatologists is keloids, which is more common in African Americans and usually found on the earlobe or chest. To treat a keloid, dense collagen needs to be softened or excised. Afterwards, continued treatment is required to prevent recurrence. There are few treatment options, and no approved treatments, making it a difficult condition to treat.

Pentoxifylline was originally an oral drug to treat vascular disorders. However, it also has anti-TNF alpha activity which can stop inflammation. Thus, it can be added to an anti-inflammatory treatment for wound or post-procedure (e.g. laser treatment) to prevent keloids from forming.

Pentoxifylline was nominated for use in combination with steroids, minoxidil, and zinc oxide. Steroids inhibit collagen from regrowing so the combination with pentoxifylline will help prevent inflammation and regrowth of collagen. Minoxidil is a hair grower and can be used with pentoxifylline for patients with hair loss or alopecia areata. oxide is a soothing paste and can act as a vehicle to deliver the drug. The combination with zinc oxide can be used for wound healing as the enzymes that repair tissues need zinc. All of these would be administered in the office.

The SME stated the proposed concentration (0.5%) is low enough not to be a safety concern. Overall, the SME stated having pentoxifylline in the office may be helpful if the practitioner takes care of many patients with skin of color for treatment of keloids.

Results of survey

One person responded to the survey on the use of pentoxifylline alone; there were 0 respondents to the surveys on the use of pentoxifylline in combination with other APIs (refer to Table 11 for respondent characteristics).

The one respondent used pentoxifylline as a topical cream for dermatologic inflammation and psoriasis. (refer to Table 12).

The survey respondent utilized compounded pentoxifylline due to lack of commercial products in an appropriate dosage form, strength or combination, other patient conditions preventing use of commercial products, and no commercially available products with pentoxifylline. Refer to Table 13 for reasons for using compounded pentoxifylline. The patient condition that prevented the respondent from using commercially available products was poor response to commercially available topical medications for psoriasis.

The one respondent did not stock non-patient-specific compounded pentoxifylline at their practice.

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	**Responses, n (N=1)**
Doctor of Medicine (MD)	1
Practice Setting	**Responses, n (N=1)**
Physician office or private practice	1

Table 12. Conditions for which pentoxifylline was prescribed or administered

Condition	**Responses, n (N=1)[a]**
Dermatologic inflammation	1
Other (psoriasis)	1

[a]Survey respondent chose one condition and provided one additional condition for which pentoxifylline was used.

Table 13. Reasons for using compounded pentoxifylline

Reason	**Responses, n (N=1)[a]**
Commercial product not available in desired dosage form, strength or combination	1
Patient allergies prevent use of commercial products	0
Patient conditions prevent use of commercial products	1
No commercial products	1
Other	0

[a]Survey respondents allowed to select multiple reasons.

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

Do you stock non-patient-specific compounded pentoxifylline products at your practice?	**Responses, n (N=1)**
Yes	0
No	1

CONCLUSION

Pentoxifylline was nominated for inclusion on the 503B Bulks List in various topical dosage forms, including but limited to cream, gel, ointment, solution, and suspension to treat inflammatory dermatologic conditions. Pentoxifylline is not available in the nominated dosage form and ROA in any of the national medical registries searched.

From the literature review and interview conducted, pentoxifylline has been used for allergic contact dermatitis, intermittent claudication, lipodermatosclerosis, nickel sensitivity, pressure ulcer, vascular disorders, wound healing, and as an anti-inflammatory treatment to prevent keloid formation. It has anti-TNF alpha activity along with anti-ischemic, antioxidant, and analgesic effects. None of the included studies used pentoxifylline in the nominated combinations, but the SME was able to provide possible reasonings behind each API mentioned in the nominated combinations. The SME did not have safety concerns regarding the nominated concentration since it is low enough and stated that pentoxifylline may be useful to have in the office for practitioners who see patients with skin of color for treatment of keloids.

The one survey respondent used pentoxifylline as a topical cream for dermatologic inflammation and psoriasis. Lack of commercial products in an appropriate dosage form, strength or combination, other patient conditions preventing use of commercial products, and no commercially available products with pentoxifylline were the reasons for using the compounded pentoxifylline product. The patient condition that prevented the survey respondent from using commercial products was poor patient response to commercially available topical medications for psoriasis. The one respondent did not stock non-patient-specific compounded pentoxifylline at their practice. There were 0 respondents to the surveys on the use of pentoxifylline in combination with other APIs.

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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 April 8, 2020
- Date last searched: April 9, 2020
- Limits: Humans (search hedge); English language
- Number of results: 206

1	pentoxifylline/	4136
2	ox?pentifyllin$.tw.	75
3	ox?pentiphyllin$.tw.	0
4	pentox#fil#n$.tw.	11
5	pentox#fyll#n$.tw.	4459
6	pentox#phyll#n$.tw.	152
7	or/1-6	5429
8	administration, topical/	38127
9	administration, cutaneous/	21846
10	topical$.tw.	103324
11	cutaneous$.tw.	149061
12	transcutaneous$.tw.	14188
13	dermal$.tw.	52184
14	transdermal$.tw.	14323
15	exp gels/	50893
16	liniments/	123
17	ointments/	12746
18	skin cream/	986
19	gel?.tw.	304821
20	liniment?.tw.	143

21	ointment?.tw.	11689
22	salve?.tw.	339
23	paste?.tw.	12202
24	unguent$.tw.	113
25	lotion?.tw.	2267
26	cream?.tw.	18571
27	betamethasone/	5895
28	minoxidil/	1546
29	niacinamide/	12374
30	exp triamcinolone/	9378
31	zinc oxide/	6701
32	betamet?ason$.tw.	4871
33	betadexamet?ason$.tw.	0
34	minossidile.tw.	0
35	minoxidil$.tw.	1799
36	minoxyl$.tw.	1
37	moxidil$.tw.	0
38	amide pp.tw.	2
39	nicotinamid$.tw.	20803
40	niacetamid$.tw.	0
41	niacinamid$.tw.	490
42	nicamid$.tw.	0
43	nicosedin$.tw.	0
44	nicotami#$.tw.	10
45	nicotinami#$.tw.	20820
46	(nicotinic adj2 amid$).tw.	92

47	nicotinoylami#$.tw.	13
48	nicotinsaureamid$.tw.	0
49	vitamin$ b3.tw.	383
50	vitamin$ pp.tw.	136
51	tranilast$.tw.	595
52	t?iamcinolon$.tw.	7588
53	tramcinolon$.tw.	3
54	triancinolon$.tw.	4
55	(zinc adj2 oxid$).tw.	7736
56	or/8-55	737989
57	and/7,56	300
58	exp animals/ not humans/	4688807
59	57 not 58	235
60	limit 59 to english language	206

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: 666

1	pentoxifylline'/de	13577
2	ox$pentifyllin*':ti,ab,tn	107
3	ox$pentiphyllin*':ti,ab,tn	1
4	pentoxifilin*':ti,ab,tn	28
5	pentoxifilen*':ti,ab,tn	0
6	pentoxyfilin*':ti,ab,tn	9
7	pentoxyfilen*':ti,ab,tn	0
8	pentoxifyllin*':ti,ab,tn	5645
9	pentoxifyllen*':ti,ab,tn	1
10	pentoxyfyllin*':ti,ab,tn	139
11	pentoxyfyllen*':ti,ab,tn	0
12	pentoxiphyllin*':ti,ab,tn	114
13	pentoxiphyllen*':ti,ab,tn	0
14	pentoxyphyllin*':ti,ab,tn	146
15	pentoxyphyllen*':ti,ab,tn	0
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	13979
17	topical drug administration'/de	81599
18	cutaneous drug administration'/de	624
19	transdermal drug administration'/de	8892
20	topical*':ti,ab	146576
21	cutaneous*':ti,ab	213926
22	transcutaneous*':ti,ab	18987

23	dermal*':ti,ab	73137
24	transdermal*':ti,ab	20865
25	cream'/de	9201
26	gel'/exp	73818
27	liniment'/de	248
28	lotion'/de	2810
29	ointment'/exp	18390
30	paste'/de	2491
31	salve'/de	165
32	cream$':ti,ab	29072
33	liniment$':ti,ab	231
34	lotion$':ti,ab	3945
35	ointment$':ti,ab	21309
36	paste$':ti,ab	14666
37	salve$':ti,ab	470
38	unguent*':ti,ab	239
39	gel$':ti,ab	357866
40	emulgel$':ti,ab	310
41	#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	921103
42	topical treatment'/de	12463
43	drug therapy'/de	718540
44	add on therapy'/de	18591
45	adjuvant therapy'/de	56556
46	drug dose':lnk	622496
47	drug administration':lnk	1725239
48	drug therapy':lnk	3858396

49	skin disease'/exp	1674803
50	therap*':ti,ab	4097803
51	treat*':ti,ab	7807528
52	betamethasone dipropionate'/de	2775
53	minoxidil'/de	7620
54	nicotinamide'/de	15717
55	triamcinolone acetonide'/de	15239
56	tranilast'/de	1509
57	zinc oxide'/de	11146
58	betamet$ason*':ti,ab,tn	7347
59	betadexamet$ason*':ti,ab,tn	0
60	minossidile':ti,ab,tn	0
61	minoxidil*':ti,ab,tn	2471
62	minoxyl*':ti,ab,tn	7
63	moxidil*':ti,ab,tn	0
64	nicotinamid*':ti,ab,tn	25246
65	niacetamid*':ti,ab,tn	0
66	niacinamid*':ti,ab,tn	776
67	nicamid*':ti,ab,tn	1
68	nicosedin*':ti,ab,tn	0
69	nicotamid*':ti,ab,tn	26
70	nicotamin*':ti,ab,tn	0
71	nicotinamin*':ti,ab,tn	21
72	nicotinamid*':ti,ab,tn	25246
73	(nicotinic NEAR/2 acid*):ti,ab,tn	9530
74	nicotinoylamin*':ti,ab,tn	18

75	nicotinoylamid*':ti,ab,tn	2
76	nicotinsaureamid*':ti,ab,tn	6
77	nikotamin*':ti,ab,tn	0
78	vitamin* b3':ti,ab,tn	461
79	vitamin* pp':ti,ab,tn	295
80	amide pp':ti,ab,tn	2
81	tranilast*':ti,ab,tn	810
82	tiamcinolon*':ti,ab,tn	4
83	triamcinolon*':ti,ab,tn	10836
84	tramcinolon*':ti,ab,tn	12
85	triancinolon*':ti,ab,tn	19
86	(zinc NEAR/2 oxid*):ti,ab,tn	7541
87	#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	12663395
88	#16 AND #41 AND #87	855
89	[animals]/lim NOT [humans]/lim	6013762
90	#88 NOT #89	793
91	#88 NOT #89 AND [english]/lim	666

Appendix 2.1 Survey instrument for use of pentoxifylline alone

Welcome. We want to understand your clinical use of compounded pentoxifylline. 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

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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 pentoxifylline to your patients?

   - o Yes
   - o No

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

   - 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 pentoxifylline for the following conditions or diseases: (check all that apply)

   - o Dermatologic inflammation
   - o Other (please explain) _____

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

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

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

7. I obtain compounded pentoxifylline 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 2.2 Survey instrument for use of pentoxifylline in combination

Welcome. We want to understand your clinical use of compounded pentoxifylline / betamethasone dipropionate / minoxidil / niacinamide as a combination product. 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.

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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 pentoxifylline / betamethasone dipropionate / minoxidil / niacinamide as a combination product to your patients?

   - o Yes
   - o No

3. Do you prescribe or administer pentoxifylline / betamethasone dipropionate / minoxidil / niacinamide as a combination product by any of the following dosage forms and/or routes of administration? (check all that apply)

   - 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 pentoxifylline / betamethasone dipropionate / minoxidil / niacinamide as a combination product for the following conditions or diseases: (check all that apply)

   - o Dermatologic inflammation
   - o Other (please explain) _____

5. I use compounded pentoxifylline / betamethasone dipropionate / minoxidil / niacinamide as a combination product 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 pentoxifylline / betamethasone dipropionate / minoxidil / niacinamide.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded pentoxifylline / betamethasone dipropionate / minoxidil / niacinamide as a combination product at your practice?

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

7. I obtain compounded pentoxifylline / betamethasone dipropionate / minoxidil / niacinamide as a combination product 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 2.3 Survey instrument for use of pentoxifylline in combination

Welcome. We want to understand your clinical use of compounded pentoxifylline / tranilast / triamcinolone acetonide as a combination product. 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.

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	Very familiar	Somewhat familiar	Not familiar
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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 pentoxifylline / tranilast / triamcinolone acetonide as a combination product to your patients?

   - o Yes
   - o No

3. Do you prescribe or administer pentoxifylline / tranilast / triamcinolone acetonide as a combination product by any of the following dosage forms and/or routes of administration? (check all that apply)

   - 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 pentoxifylline / tranilast / triamcinolone acetonide as a combination product for the following conditions or diseases: (check all that apply)

   - o Dermatologic inflammation
   - o Other (please explain) _____

5. I use compounded pentoxifylline / tranilast / triamcinolone acetonide as a combination product 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 pentoxifylline / tranilast / triamcinolone acetonide.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded pentoxifylline / tranilast / triamcinolone acetonide as a combination product at your practice?

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

7. I obtain compounded pentoxifylline / tranilast / triamcinolone acetonide as a combination product 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 2.4 Survey instrument for use of pentoxifylline in combination

Welcome. We want to understand your clinical use of compounded pentoxifylline / tranilast / triamcinolone acetonide / zinc oxide as a combination product. 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.

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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 pentoxifylline / tranilast / triamcinolone acetonide / zinc oxide as a combination product to your patients?

   - o Yes
   - o No

3. Do you prescribe or administer pentoxifylline / tranilast / triamcinolone acetonide / zinc oxide as a combination product by any of the following dosage forms and/or routes of administration? (check all that apply)

   - 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 pentoxifylline / tranilast / triamcinolone acetonide / zinc oxide as a combination product for the following conditions or diseases: (check all that apply)

   - o Dermatologic inflammation
   - o Other (please explain) _____

5. I use compounded pentoxifylline / tranilast / triamcinolone acetonide / zinc oxide as a combination product 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 pentoxifylline / tranilast / triamcinolone acetonide / zinc oxide.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded pentoxifylline / tranilast / triamcinolone acetonide / zinc oxide as a combination product at your practice?

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

7. I obtain compounded pentoxifylline / tranilast / triamcinolone acetonide / zinc oxide as a combination product 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.