Summary Report

Enalapril maleate

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
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 enalapril maleate (UNII code: 9O25354EPJ), 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 enalapril maleate 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 enalapril maleate 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 enalapril maleate 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

Enalapril maleate was nominated for inclusion on the 503B Bulks List by Triangle Compounding Pharmacy, Inc. Enalapril maleate was nominated for hypertension and congestive heart failure via oral capsules and suspension, and transdermal creams and gels. On further investigation of the nomination and consultation with a veterinarian, it was determined that the transdermal route of administration (ROA) was likely for animal use.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of enalapril maleate.[6-8]

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

- Allergies and intolerances to inactive ingredients
- Patient's inability to swallow tablets
- Tablets are not appropriate for transdermal preparations

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of enalapril maleate 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, 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 enalapril maleate; name variations of enalapril maleate 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 enalapril maleate. 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: enalapril maleate and transdermal administration (refer to Appendix 1 for full search strategies). Oral administration was not considered for the literature review due to the availability of FDA-approved oral enalapril products. 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 April 5, 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 5, 2020 for clinical practice guidelines that recommended the use of enalapril maleate 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 enalapril maleate 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 enalapril maleate 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 enalapril maleate 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 enalapril maleate; setting; total number of patients; number of patients who received enalapril maleate; patient population; indication for use of enalapril maleate; dosage form and strength; dose; ROA; frequency and duration of

therapy; use of enalapril maleate in a combination product; use and formulation of enalapril maleate in a compounded product; use of enalapril maleate 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 enalapril maleate 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 enalapril maleate: cardiology, pediatrics and neonatology, 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. 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 enalapril maleate 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

- Enalapril maleate is not available as an FDA-approved product in the nominated dosage forms and ROA.
- Enalapril maleate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for enalapril maleate.
- Enalapril maleate is not available in the nominated dosage forms 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 245 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 215 titles and abstracts were screened. After screening, the full text of 16 articles was reviewed. Finally, 0 studies were included. Sixteen (16) studies were excluded for the following reasons: wrong study design (8 studies); wrong indication (4); wrong dosage form or ROA (2); wrong intervention (1); unable to obtain (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.

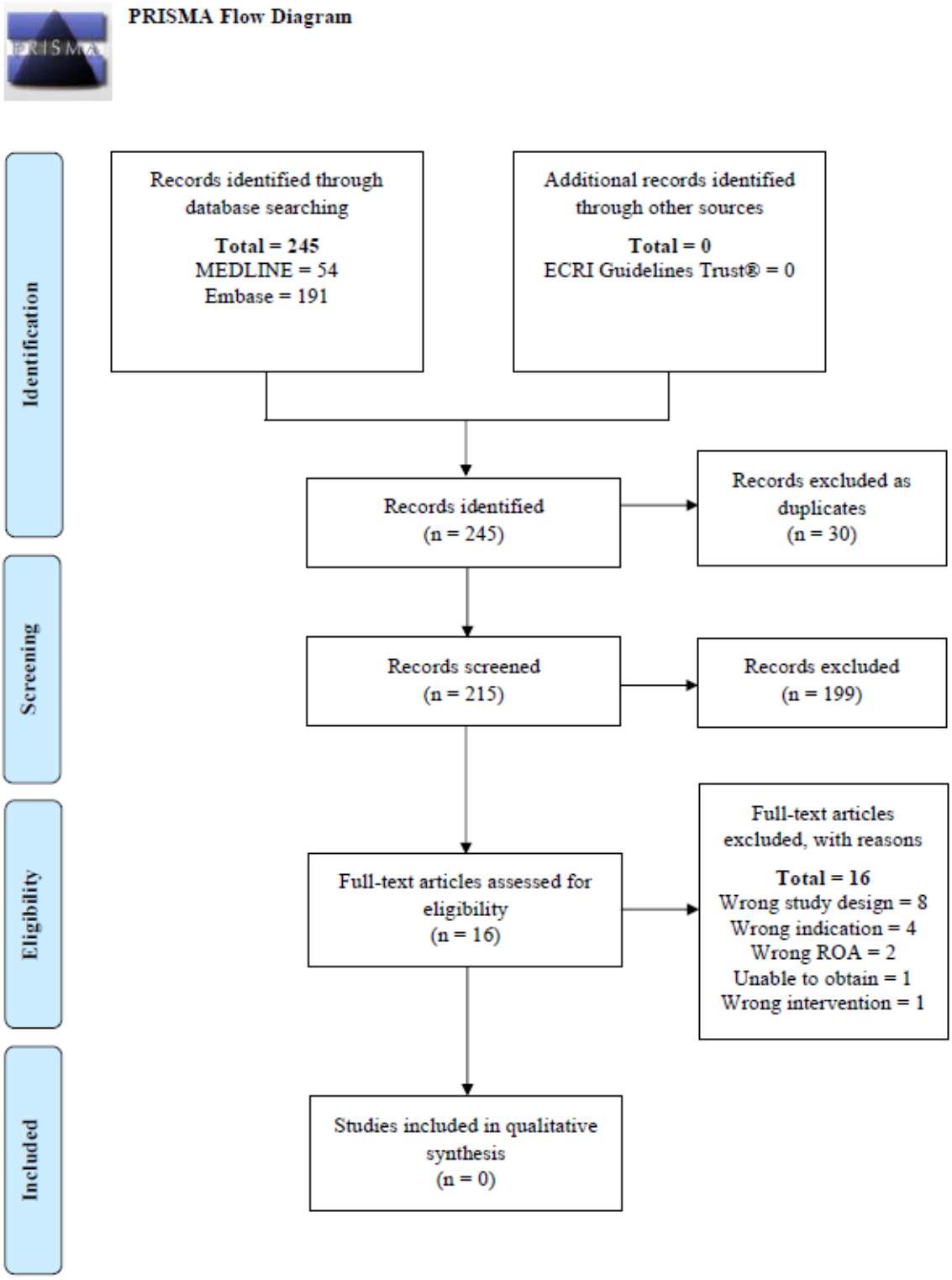
Use of enalapril maleate

No studies were included from the literature review.

Pharmacology and historical use

No additional references were found that provided information about the pharmacology or historical use of enalapril maleate as a transdermal preparation.

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 combinations

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. Four SMEs discussed enalapril maleate. The 4 SMEs were all medical doctors. The SMEs specialized and/or were board-certified in cardiology and primary care and family medicine, working in academic medical practice. The SMEs had been in practice for 19 to 33 years.

One SME stated that enalapril is used primarily for infants with pulmonary hypertension, but it is not the first line drug. Another SME stated that they use lisinopril instead because enalapril has a twice a day dosing, while lisinopril has once a day dosing with the same effect; the SME was not aware of anyone that uses enalapril.

When it comes to compounding, the SMEs had never seen a need for compounding any formulation of enalapril and to the SME's knowledge, they have never encountered a patient who had an allergy to an inactive ingredient.

Three SMEs discussed the dosage forms. Infants or young children would be able to take an oral suspension better than solid dosage forms. When asked about transdermal dosage forms, one SME stated with uncertainty that maybe they could be used for patients who cannot take pills. Another SME said that they might consider using a patch, but not a cream or gel. One SME mentioned that they would never use transdermal enalapril but could see it being used for dogs.

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 enalapril maleate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded enalapril maleate

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded enalapril maleate

No respondents to survey distributed via professional medical associations

CONCLUSION

Enalapril maleate was nominated for inclusion on the 503B Bulks List as oral capsules and suspensions, and transdermal creams and gels to treat hypertension and congestive heart failure. Enalapril maleate is not available in the nominated dosage forms and ROA in any of the foreign registries searched.

From the literature review and interviews conducted, enalapril can be used for pulmonary hypertension but it is not the first line drug. Also, there are other options available, such as lisinopril, that require less frequent dosing than enalapril, so enalapril is not used much. SMEs had not used compounded enalapril and had never encountered a patient who would need a compounded product due to an allergy to an inactive ingredient. The SMEs stated that an oral suspension would be better for pediatric patients than a solid dosage form. As for transdermal dosage forms, one SME would use a patch but not cream or gel, and another SME would never use it, but can see it being used for dogs.

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 April 3, 2020
- Date last searched: April 5, 2020
- Limits: Humans (search hedge); English language
- Number of results: 54

1	enalapril/	6093
2	analapril$.tw.	3
3	enalapril$.tw.	7244
4	or/1-3	8755
5	administration, topical/	38106
6	administration, cutaneous/	21834
7	topical$.tw.	103235
8	cutaneous$.tw.	148988
9	transcutaneous$.tw.	14179
10	dermal$.tw.	52116
11	transdermal$.tw.	14298
12	exp gels/	50857
13	skin cream/	985
14	emulsions/	17705
15	liniments/	123
16	ointments/	12745
17	emulsion?.tw.	32210
18	gel?.tw.	304409
19	liniment?.tw.	143
20	ointment?.tw.	11675

21	salve?.tw.	338
22	paste?.tw.	12184
23	unguent$.tw.	112
24	lotion?.tw.	2264
25	cream?.tw.	18553
26	or/5-25	716618
27	and/4,26	95
28	exp animals/ not humans/	4686014
29	27 not 28	60
30	limit 29 to english language	54

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: April 5, 2020
- Limits: Humans (search hedge); English language
- Number of results: 191

1	enalapril'/de	26084
2	enalapril*':ti,ab,tn	9657
3	analapril*':ti,ab,tn	16
4	#1 OR #2 OR #3	28058
5	topical drug administration'/de	81608
6	cutaneous drug administration'/de	620
7	transdermal drug administration'/de	8894
8	topical treatment'/de	12462
9	topical*':ti,ab	146566
10	transcutaneous*':ti,ab	18988
11	dermal*':ti,ab	73131
12	transdermal*':ti,ab	20865
13	cream'/de	9201
14	gel'/exp	73810
15	liniment'/de	248
16	lotion'/de	2810
17	ointment'/exp	18393
18	paste'/de	2490
19	salve'/de	165
20	emulsion'/exp	44335
21	cream$':ti,ab	29070
22	emulsion$':ti,ab	44035

23	lotion$':ti,ab	3945
24	ointment$':ti,ab	21306
25	paste$':ti,ab	14665
26	salve$':ti,ab	470
27	unguent*':ti,ab	239
28	liniment*':ti,ab	239
29	gel$':ti,ab	357854
30	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	789346
31	#4 AND #30	248
32	[animals]/lim NOT [humans]/lim	6013410
33	#31 NOT #32	205
34	#31 NOT #32 AND [english]/lim	191

Appendix 2. Survey instrument for professional medical associations

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

   - o Yes
   - o No

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

   - o Oral capsule
   - o Oral suspension
   - o Transdermal cream
   - o Transdermal gel
   - o None of the above

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

   - o Congestive heart failure
   - o Hypertension
   - o Other (please explain) _____

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

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

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

7. I obtain compounded enalapril maleate 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 who declined in Year 1 were not contacted in Year 2.