

# Summary Report

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## Menthol

### Prepared for:

Food and Drug Administration

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

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## REVIEW OF NOMINATIONS

Menthol (UNII code: L7T10EIP3A) was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA) and Sincerus Florida, LLC. While the exact medical condition for which the compounded product is being requested is generally unknown, menthol is generally used to treat pruritus. Menthol was nominated for use as a topical spray or gel in strengths from 1-2%, or in dosage forms and strengths based on the prescriber's request.

Menthol was nominated for use in combination with other active pharmaceutical ingredients (API), refer to Table 7 for the specific nominated formulations.

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

- Patients respond differently to drug products and the compounded product may be the only formulation to effectively treat the indication for which it is intended to treat.
- Compounding from bulk ensures that only the ingredients necessary to achieve the desired clinical outcome eliminating any fillers, excipients, binders, dyes, preservatives, or other materials that may be irritating, hazardous, or allergenic.
- Commercially available finished products have an inherent variance in potency creating an uncertain final concentration for the new product.
- Commercially available products with menthol contain additional API that are not in the proposed compounded formulations or would not be able to be compounded into the proposed dosage forms.

## METHODOLOGY

### *Background information*

The national medicine registers of 13 countries and regions were searched to establish the availability of menthol 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 menthol; name variations of menthol 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(s); strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms and/or ROAs similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing menthol. 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

Two databases (PubMed and Embase) were searched including any date through June 6, 2019. The search included a combination of (menthol[TIAB] OR mentol[TIAB] OR cyclohexanol[TIAB]) AND (desoximetasone[TIAB] OR pramoxine[TIAB] OR tranilast[TIAB] OR “betamethasone dipropionate”[TIAB] OR hydrocortisone[TIAB] OR “levocetirizine dihydrochloride”[TIAB] OR spray OR gel OR topical OR ointment) AND humans[MeSH Terms] AND English[lang] NOT autism. Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

### Study selection

Articles were not excluded on the basis of study design. Menthol is a component of an FDA-approved product, as a result, articles were excluded if menthol was utilized as the FDA-approved product or in the same concentration and formulation as the FDA-approved product. Articles were considered relevant based on the identification of a clinical use of menthol or the implementation of menthol in clinical practice. Articles were excluded if not in English, a clinical use was not identified, incorrect salt form, or if the study was not conducted in humans. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

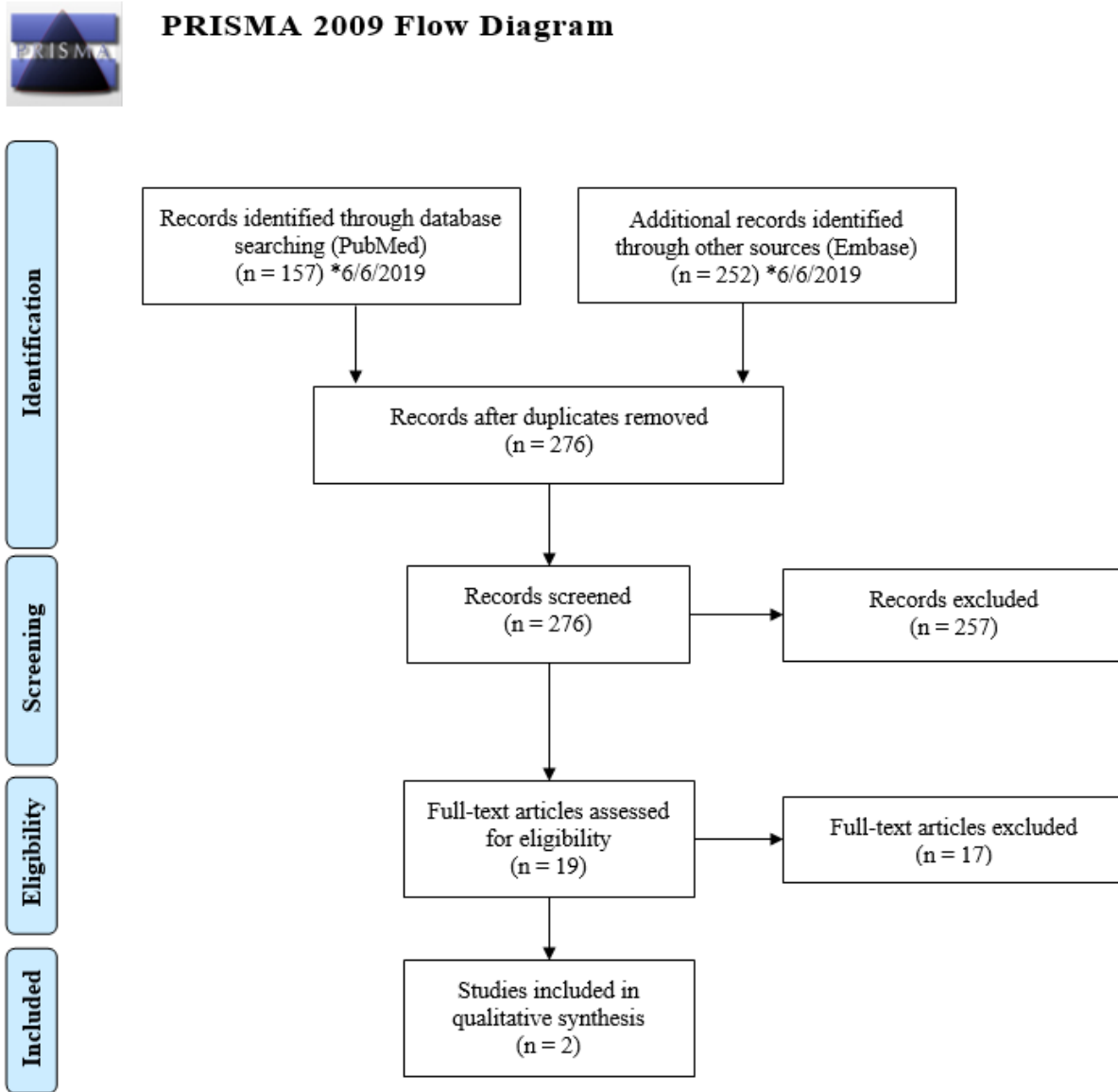
### Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for menthol use; dose; strength; dosage form; ROA; frequency and duration of therapy; any combination therapy utilized; if applicable, formulation of compounded products; study design; and any discussion surrounding the use of menthol compared to alternative therapies.

### Results

Please refer to Figure 1.

Figure 1. Summary of literature screening and selection (PRISMA 2009 Flow Diagram)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit [www.prisma-statement.org](http://www.prisma-statement.org).

### *Outreach to medical specialists and specialty organizations*

Using the indications from the nominations and the results of the literature review, three (3) medical specialties that would potentially use menthol were identified: dermatology, podiatry, and primary care. Semi-structured interviews were conducted with subject matter experts within these specialties. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. One (1) expert was contacted for interviews, of which one (1) accepted and zero (0) declined interviews. The interview was recorded and transcribed via ©Rev.com. QSR International’s Nvivo 12 software was utilized for qualitative data analysis. The University of Maryland, Baltimore IRB and the Food & Drug Administration R1HSC reviewed the study and found it to be exempt. Subject matter experts provided their oral informed consent to participate in interviews.

### *Survey*

General professional medical associations and specialty associations for dermatology, podiatry, and primary care, identified from the nominations, were contacted to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within each specialty. Associations were included if their members are predominantly practitioners, national associations, and organizations focused on practice within the US. Organizations without practicing physicians and state or regional organizations were excluded. The association’s website was searched in order 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 online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to eight (8) associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

Participation was anonymous and voluntary. The estimated time for completion was 30 minutes with a target of 50 responses per survey. The Office of Management and Budget (OMB) approved this project.

Table 1. Participating associations

<b>Specialty</b>	<b>Association</b>
Dermatology	American Academy of Dermatology (AAD)
	American Society for Dermatologic Surgery (ASDS)
Primary Care	American Academy of Environmental Medicine (AAEM)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Podiatry	American Podiatric Medical Association (APMA)	Failed to respond
Primary Care	American College of Physicians (ACP)	Failed to respond
	American Academy of Family Physicians (AAFP)	Failed to respond

## CURRENT AND HISTORIC USE

### *Summary of background information*

- Menthol is not available as an FDA-approved product.
- Menthol is available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for menthol.
- Menthol is available in Abu Dhabi (see Table 4).

Table 3. Currently approved products – US

*No approved products in the US*

Table 4. Currently approved products – select non-US countries and regions<sup>a</sup>

Active Ingredient	Concentration	Dosage Form	ROA	Approved For Use		
				Country	Status	Approval Date
Menthol	3.15%, 4%	Gel	Topical	Abu Dhabi	Active	–
	10%	Spray				

Abbreviations: “–”, not mentioned; ROA, route of administration.

<sup>a</sup>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 ROAs similar to those requested in the nominations. See Methodology for full explanation.

*Summary of literature review*

There was one (1) experimental study found from the US for the treatment of ankle sprain. There was also one (1) descriptive study in the US for treating pruritus.

Table 5. Types of studies

Types of Articles	Number of Studies
Descriptive <sup>1</sup>	1
Experimental <sup>2</sup>	1
Observational	0

Table 6. Number of studies by country

Country	Number of Studies
US <sup>1,2</sup>	2
Total US: 2 Total Non-US Countries: 0	

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
<b>Nominated</b>	Menthol 1% / hydrocortisone 2.5% / levocetirizine dihydrochloride 2%	0
	Menthol 2% / betamethasone dipropionate 0.05% / pramoxine 1% / tranilast 0.5%	0
	Menthol 2% / desoximetasone 0.05% / pramoxine 1% / tranilast 0.5%	0
<b>Others found in literature</b>	Menthol 0.5% / camphor 0.5% – topical lotion <sup>1</sup>	1
	Menthol 0.09% -3% / diclofenac 1% – topical gel <sup>2</sup>	1

Table 8. Dosage by indication – US

<b>Indication</b>	<b>Dose</b>	<b>Concentration</b>	<b>Dosage Form</b>	<b>ROA</b>	<b>Duration of Treatment</b>
Ankle sprain <sup>2</sup>	16g/day	0.09%-3%	Gel	Topical	Up to 10 days
Pruritis <sup>1</sup>	–	0.5%	Lotion	Topical	1 month

Abbreviations: “–”, not mentioned; ROA, route of administration.

Table 9. Dosage by indication – non-US countries

*No studies included from non-US countries*

Table 10. Compounded products – US

*No compounded products from reported studies*

Table 11. Compounded products – non-US countries

*No compounded products from reported studies*

*Summary of focus groups/interviews of medical experts and specialty organizations*

One (1) interview was conducted.

Table 12. Overview of interviewee

<b>Interviewee</b>	<b>Level of Training</b>	<b>Specialty</b>	<b>Current Practice Setting</b>	<b>Experience with Menthol</b>	<b>Interview Summary Response</b>
DER_07	MD	Dermatology Dermatology/Immunology	Independent consultant	Not specified	<ul style="list-style-type: none"> <li>Describes menthol as “an old-time remedy” for treating itching.</li> </ul>

Abbreviation: MD, Doctor of Medicine.

Use of menthol

- One (1) interviewee stated that there are a limited number of antipruritic drugs; in the past, labels were not able to include if they treat itch, since that was considered a symptom of an underlying disease state that needed treatment. Itch was not considered an important aspect to treat to improve the patient’s quality of life until the PDUFA re-authorization.
  - Menthol is an “old-time remedy” as an anti-itch product.

Compounding menthol versus OTC products

- The interviewee said that the purpose behind the combinations nominated for menthol are likely in attempt to increase the anti-itch benefit by adding in other antipruritic agents that may or may not be approved as independent products. But there is no data to confirm improved efficacy over what is currently available.
  - It comes down to what the provider likes and what the patient has already tried. These combinations might come out after the patient has tried an OTC product and not received adequate relief.

Menthol as office stock

- The interviewee said, “I am almost positive that it’s got to be for dispensing. I cannot envision a scenario in which someone’s going to come in to me for itch and I’m going to put it on in the office and cure them and they’re done. But with that inflammatory disorder – psoriasis, eczema, you name it, they’re going to continue to have it. My guess it they’re going home with this.”
  - This is more of a long-term treatment rather than short-term.

*Summary of survey results*

Table 13. Characteristics of survey respondents [4 people responded to the survey.]

<b>Board Certification</b>	<b>MD</b>	<b>No Response</b>
Dermatology	1	0
No Response	0	3

Abbreviation: MD, Doctor of Medicine.

Table 14. Types of products used, prescribed, or recommended

<b>Types of Products</b>	<b>Respondents, n (N=1<sup>a</sup>)</b>
Compounded	0
FDA-approved	0
Over-the-counter	0
Dietary	0
Unsure	0
No Response	1

<sup>a</sup>Out of four (4) respondents, one (1) reported using, prescribing, or recommending menthol products.

Table 15. Compounded use of menthol in practice

*No survey respondents provided this information*

Table 16. Indications for which menthol is considered a standard therapy

*No survey respondents provided this information*

Table 17. Reasons for using compounded product instead of the FDA-approved products

*No survey respondents provided this information*

Table 18. Change in frequency of compounded menthol usage over the past 5 years

*No survey respondents provided this information*

Table 19. Do you stock non-patient specific compounded menthol in your practice?

*No survey respondents provided this information*

Table 20. Questions related to stocking non-patient specific compounded menthol

*No survey respondents provided this information*

## **CONCLUSION**

Menthol (UNII code: L7T10EIP3A) was nominated for inclusion on the 503B Bulks List and while the exact medical condition for which the compounded product is being requested is generally unknown, menthol is generally used to treat pruritus. Menthol was nominated for use as a topical spray or gel in strengths from 1-2%, or in dosage forms and strengths based on the prescriber's request. Menthol is available in Abu Dhabi and as an OTC product in the US.

From the literature review conducted, two (2) US studies provided indications for menthol with the treatment of ankle sprain and pruritus in combination with diclofenac and camphor, respectively.

The interviewee did not specify experience with menthol, only described it as "pretty old school".

From the survey responses, one (1) out of four (4) respondents reported using, prescribing, or recommending menthol in practice, but did not specify the type of product.

## APPENDICES

### *Appendix 1. References*

1. Haight JM, Jukic DM, English III JC. Hydroxyethyl starch-induced pruritus relieved by a combination of menthol and camphor. *J Am Acad Dermatol*. 2008;59(1):151-153.
2. Lai PM, Collaku A, Reed K. Efficacy and safety of topical diclofenac/menthol gel for ankle sprain: a randomized, double-blind, placebo- and active-controlled trial. *J Int Med Res*. 2017;45(2):647-661.

## Appendix 2. Survey instrument

### Start of Block: Welcome Page

The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice. This survey is for **menthol**. As a medical expert, we appreciate your input regarding the use of this substance in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871

Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. 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. If you have additional questions or concerns about this research study, please email: [compounding@rx.umaryland.edu](mailto: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](mailto:hrpo@umaryland.edu).

### End of Block: Welcome Page

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### Start of Block: Menthol

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **menthol**? Please check all that apply.

- Compounded drug product
- FDA-approved drug product
- Over the counter drug product
- Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- Unsure

*Skip To: Q13. If What type(s) of product(s) do you use, prescribe, or recommend for menthol?... != Compounded drug product Is Not Selected*

*Skip To: Q2. If What type(s) of product(s) do you use, prescribe, or recommend for menthol?... = Compounded drug product Is Selected*

*Display This Question:*

*If What type(s) of product(s) do you use, prescribe, or recommend for menthol?... = Compounded drug product*

Q2. Please list any conditions or diseases for which you use compounded **menthol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q3. Do you use compounded **menthol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- Single
- Combination

*Skip To: Q5. If Do you use compounded menthol as a single agent active ingredient, or as on... != Combination Is Not Selected*

*Display This Question:*

*If Loop current: Do you use compounded menthol as a single agent active ingredient, or as on... = Combination Is Selected*

Q4. In which combination(s) do you use compounded **menthol**? Please check all that apply.

- Menthol 1% / Hydrocortisone 2.5% / Levocetirizine dihydrochloride 2%
- Menthol 2% / Betamethasone dipropionate 0.05% / Pramoxine 1% / Tranilast 0.5%
- Menthol 2% / Desoximetasone 0.05% / Pramoxine HCl 1% / Tranilast 0.5%
- Other (please describe) \_\_\_\_\_

Q5. For which, if any, diseases or conditions do you consider compounded **menthol** standard therapy?

\_\_\_\_\_

Q6. Does your specialty describe the use of compounded **menthol** in medical practice guidelines or other resources?

\_\_\_\_\_

Q7. Over the past 5 years, has the frequency in which you have used compounded **menthol** changed?

- Yes - I use it **MORE** often now (briefly describe why) \_\_\_\_\_
- Yes - I use it **LESS** often now (briefly describe why) \_\_\_\_\_
- No - use has remained consistent

Q8. Why do you use compounded **menthol** instead of any FDA-approved drug product?

\_\_\_\_\_

Q9. Do you stock non-patient-specific compounded **menthol** in your practice location?

- Yes
- No

*Skip To: End of Block If Do you stock non-patient-specific compounded menthol in your practice locat... = No*

*Display This Question:*

*If Do you stock non-patient-specific compounded menthol in your practice locat... = Yes*

Q10. In what practice location(s) do you stock non-patient-specific compounded **menthol**? Please check all that apply.

- Physician office
- Outpatient clinic
- Emergency room
- Operating room
- Inpatient ward
- Other (please describe) \_\_\_\_\_

Q11. How do you obtain your stock of non-patient-specific compounded **menthol**? Please check all that apply.

- Purchase from a compounding pharmacy
- Purchase from an outsourcing facility
- Compound the product yourself
- Other (please describe) \_\_\_\_\_

Q12. Why do you keep a stock of non-patient-specific compounded **menthol**? Please check all that apply.

- Convenience
- Emergencies
- Other (please describe) \_\_\_\_\_

*Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded menthol? Please... = Convenience*

*Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded menthol? Please... = Emergencies*

*Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded menthol? Please... = Other (please describe)*

Q13. For which, if any, diseases or conditions do you consider **menthol** standard therapy?

\_\_\_\_\_

Q14. Does your specialty describe the use of **menthol** in medical practice guidelines or other resources?

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End of Block: Menthol

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Start of Block: Background Information

Q15. What is your terminal clinical degree? Please check all that apply.

- Doctor of Medicine (MD)
- Doctor of Osteopathic Medicine (DO)
- Doctor of Medicine in Dentistry (DMD/DDS)
- Naturopathic Doctor (ND)
- Nurse Practitioner (NP)
- Physician Assistant (PA)
- Other (please describe) \_\_\_\_\_

Q16. Which of the following Board certification(s) do you hold? Please check all that apply.

- No Board certification
- Allergy and Immunology
- Anesthesiology
- Cardiovascular Disease
- Critical Care Medicine
- Dermatology
- Emergency Medicine
- Endocrinology, Diabetes and Metabolism
- Family Medicine
- Gastroenterology
- Hematology
- Infectious Disease
- Internal Medicine
- Medical Toxicology
- Naturopathic Doctor
- Naturopathic Physician
- Nephrology
- Neurology
- Obstetrics and Gynecology
- Oncology
- Ophthalmology
- Otolaryngology
- Pain Medicine
- Pediatrics
- Psychiatry
- Rheumatology
- Sleep Medicine
- Surgery (please describe) \_\_\_\_\_

Urology

Other (please describe) \_\_\_\_\_

**End of Block: Background Information**