Summary Report

Clioquinol

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

Clioquinol (UNII code: 7BHQ856EJ5) was nominated for inclusion on the 503B Bulks List by Sincerus Florida, LLC and the Outsourcing Facilities Association (OFA). While the exact medical condition for which the compounded product is generally unknown, clioquinol is generally used as an antifungal or antiprotozoal drug. Clioquinol is nominated for use as a topical product in various dosage forms based on the prescriber's request including, but not limited to gels, creams, ointments, solutions, and suspensions at strengths based on the prescriber's request; the therapeutic dose is 1%. Clioquinol has been used previously to compound a topical combination ingredient cream that contains clioquinol 1%, coal tar solution 2%, hydrocortisone 1%, metronidazole 2%, and salicylic acid 2%.

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

- The dosage form, strength, or flavor of a commercially available FDA-approved product may be inappropriate for the patient.
- Commercially available products may contain excipients, fillers, or preservatives that cannot be tolerated by the patient due to sensitives or allergies to these ingredients.
- Commercially available finished products have an inherent variance in potency creating an uncertain final concentration for the new product.
- There are no FDA-approved products containing this active pharmaceutical ingredient (API).

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of clioquinol 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 clioquinol; name variations of clioquinol 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 ROA 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 clioquinol. 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 February 27, 2019. The search included a combination of (clioquinol[TIAB] OR iodochlorhydroxyquin[TIAB] OR iodochloroxyquinoline[TIAB] OR "5 chloro 7 iodo 8 quinolinol"[TIAB] OR chinoform[TIAB]) AND (cream 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 RefWorks®, merged, and sorted for removal of duplicate citations. Covidence® was used for screening purposes.

Study selection

Articles were not excluded on the basis of study design. Clioquinol is a component of an FDA-approved product that has been discontinued by the manufacturer, not for safety or efficacy reasons. As a result, articles were excluded if clioquinol was utilized as the FDA-approved product or in the same concentration and formulation as the FDA-approved product. Additional exclusion criteria include any dosage form/ROA that differed from the nominated dosage form/ROA. Articles were considered relevant based on the identification of a clinical use of clioquinol or the implementation of clioquinol 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.

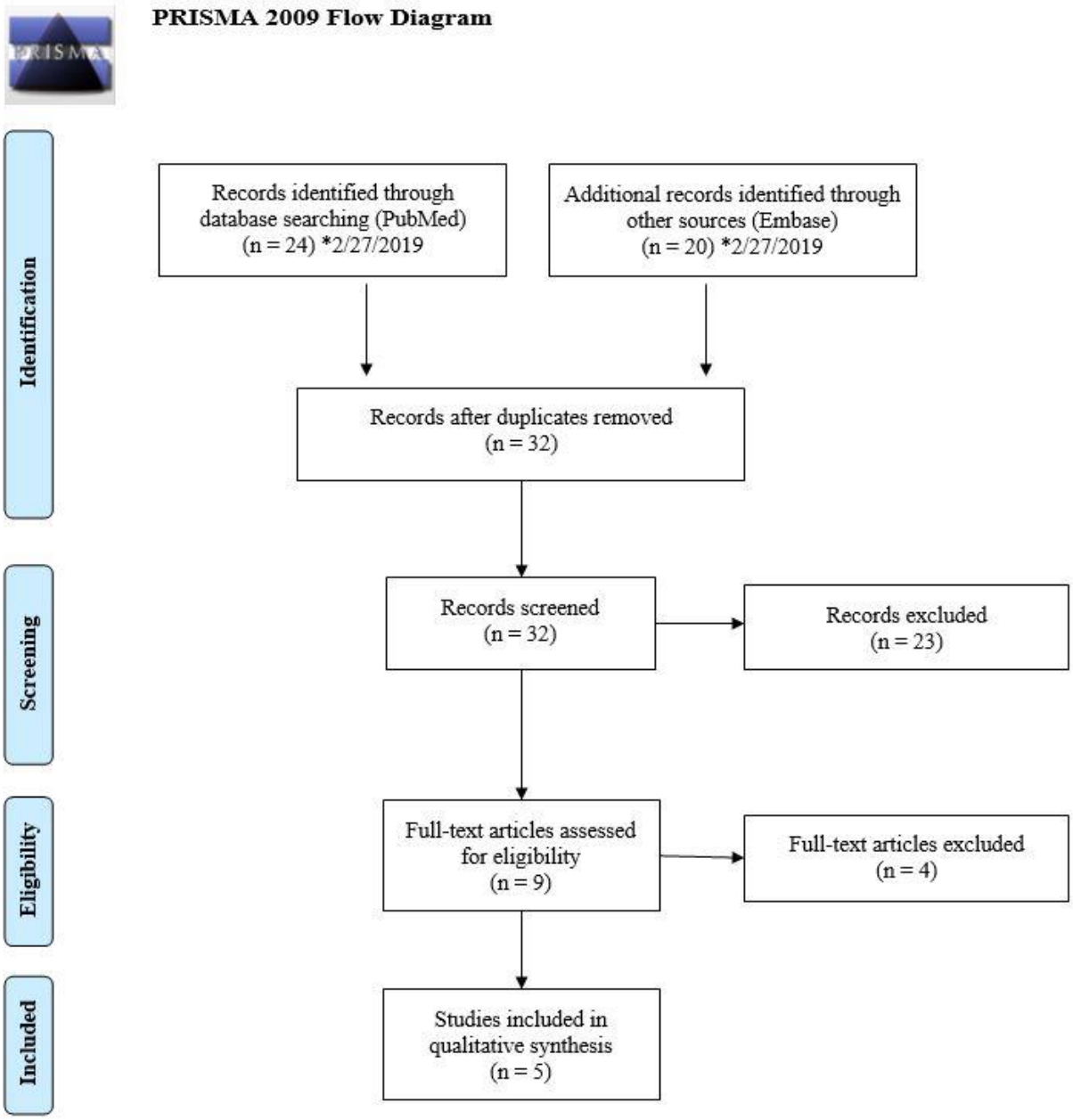
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for clioquinol 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 clioquinol 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). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Outreach to medical specialists and specialty organizations

Using the indications from the nominations and the results of the literature review, two (2) medical specialty that would potentially use clioquinol was identified: dermatology and infectious disease. Semi-structured interviews were conducted with subject matter experts within this specialty. 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 RIHSC 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 and infectious disease, identified from the nominations, literature review, and interview, 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 five (5) 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

Specialty	Association
Dermatology	American Academy of Dermatology (AAD)
	American Society for Dermatologic Surgery (ASDS)

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

CURRENT AND HISTORIC USE

Summary of background information

- Clioquinol is not available as an FDA-approved product.
- Clioquinol is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for clioquinol.
- Clioquinol is not available in any of the national medical registries searched. Clioquinol is available as a topical OTC product in Canada.

Table 3. Currently approved products – US

No approved products in the US

Table 4. Currently approved products – select non-US countries and regions

No approved products in select non-US countries and regions

Summary of literature review

- Total number of studies included: 5 experimental studies.
- Indications included cutaneous fungal infection, nickel-induced hypersensitivity, psoriasis and dermatoses, secondarily infected dermatoses, and ulcer in leprosy.
- Compounded clioquinol as a topical ointment were identified from one (1) non-US study for nickel-induced hypersensitivity.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive	0
Experimental[1-5]	5
Observational	0

Table 6. Number of studies by country

Country	Number of Studies
India[1]	1
Mexico[4]	1
Norway[5]	1
UK[3]	1
US[2]	1
	Total US: 1 Total non-US Countries: 4

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Clioquinol 1% / Coal tar solution 2% / Hydrocortisone 1% / Metronidazole 2% / Salicylic acid 2%	0

Table 7. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Cutaneous fungal infection[2]	–	3%	Cream	Topical	7 days

Abbreviation: ROA, route of administration.

Table 8. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Nickel-induced hypersensitivity[3]	50-200mg	10%	Cream, Ointment	Topical	48 hours
Psoriasis, dermatoses[5]	–	3%	Ointment	Topical	3 weeks
Secondarily infected dermatoses[1]	–	3%	Cream	Topical	4 weeks
Ulcer in leprosy[4]	–	3%	Cream	Topical	3 months

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

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
Nickel-induced hypersensitivity[3]	• Clioquinol in yellow soft paraffin	Ointment	0.3%-10%

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

One (1) interview was conducted.

Table 11. Overview of interviewee

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Clioquinol	Interview Summary Response
DER_06	MD	Dermatology Dermatology/Immunology	Independent consultant	Not specified	• Clioquinol is a known anti-fungal

Abbreviation: MD, Doctor of Medicine.

Use of clioquinol

- One interviewee responded "Another one where okay, it's available, it's a known anti-fungal, why are we making it in these combos for somebody to use in a doctor's office, unless they're dispensing it? It's not a one-time use product."

Use as a combination product

- The interviewee responded "well anti-hydrocortisone is not inconsistent with what we have. So you think about people have for a long time had topical steroid plus anti-fungal. The place that made me nuts as a physician was family practitioners who would see a rash, don't know what it is, and they would write for a combo triamcinolone anti-fungal because of course that would treat it if it was fungus or treat it if it was an inflammatory skin condition and they just didn't know which one it was. That to me is lazy science. Some patients with fungal infections on their feet have a fair amount of inflammation and itch, so putting hydrocortisone with it will make it better. Metronidazole is a much more effective anti-fungal product. The coal tar, that's really an interesting idea. I don't know where that's coming from. Coal tar was mostly used for psoriasis, it's not much used much for contact dermatitis. It's not used much for fungal infection…Salicylic acid, keratolytic. Using anti-fungals and keratolytics together is not uncommon because you're trying to get rid of that superficial scale and taking the scale off helps make the drug work better. I can understand that, but again, why are we using it in somebody's office as opposed to write a prescription and let them go get it filled at some prescribing pharmacy."

Summary of survey results

Table 12. Characteristics of survey respondents [5 people responded to the survey.]

Board Certification	MD	No Response
Dermatology	2	0
No Response	0	3

Abbreviation: MD, Doctor of Medicine.

Table 13. Types of products used, prescribed, or recommended

No survey respondents provided this information

Table 14. Compounded use of clioquinol in practice

No survey respondents provided this information

Table 15. Indications for which clioquinol is considered a standard therapy

No survey respondents provided this information

Table 16. Reasons for using compounded product instead of the FDA-approved products

No survey respondents provided this information

Table 17. Change in frequency of compounded clioquinol usage over the past 5 years

No survey respondents provided this information

Table 18. Do you stock non-patient specific compounded clioquinol in your practice?

No survey respondents provided this information

Table 19. Questions related to stocking non-patient specific compounded clioquinol

No survey respondents provided this information

CONCLUSION

Clioquinol (UNII code: 7BHQ856EJ5) was nominated for inclusion on the 503B Bulks List. While the exact medical condition for which the compounded product is generally unknown, clioquinol is generally used as an antifungal or antiprotozoal drug. Clioquinol is nominated for use as a topical product in various dosage forms based on the prescriber's request including, but not limited to gels, creams,

ointments, solutions, and suspensions at strengths based on the prescriber's request; the therapeutic dose is 1%. Clioquinol is not available in any of the national medical registers that were reviewed, but is available in Canada as a topical OTC product.

From the literature review conducted, the only indication from a US study was cutaneous fungal infection. Other indications from non-US sources included nickel-induced hypersensitivity, psoriasis and dermatoses, secondarily infected dermatoses, and ulcer in leprosy. One (1) non-US study reported using compounded clioquinol as a topical ointment used for nickel-induced hypersensitivity.

The interviewee did not specify experience with clioquinol, just stated that it is a known anti-fungal and that it is not a one-time use product.

From the survey, none of the five (5) respondents reported using, prescribing, or recommending clioquinol in practice.

APPENDICES

Appendix 1. References.

1. Chattopadhyay SP, Arora PN, Anand S, Sharma SD. Betamethasone dipropionate (0.05)% plus chinoform (3%) cream against betamethasone valerate (0.1%) plus chinoform cream (3%) in secondarily infected dermatoses. *Indian journal of dermatology.* 1987;32(3):73-76.
2. Maibach HI. Iodochlorhydroxyquin-hydrocortisone treatment of fungal infections. Double-blind trial. *Archives of dermatology.* 1978;114(12):1773-1775.
3. Memon AA, Molokhia MM, Friedmann PS. The inhibitory effects of topical chelating agents and antioxidants on nickel-induced hypersensitivity reactions. *Journal of the American Academy of Dermatology.* 1994;30(4):560-565.
4. Salazar JJ, Serrano GG, Leon-Quintero GI, Torres-Mendoza BM. Use of topical ketanserin for the treatment of ulcers in leprosy patients. *Indian Journal of Leprosy.* 2001;73(2):103-110.
5. Tollofsrud A. Dermatologic investigation of betamethasone 17,21-dipropionate ointment with chinoform. *The Journal of international medical research.* 1977;5(2):132-135.

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

End of Block: Welcome Page

Start of Block: Clioquinol

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **clioquinol**? 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 clioquinol?... != Compounded drug product Is Not Selected

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

Display This Question:

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

Q2. Please list any conditions or diseases for which you use compounded **clioquinol** 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 **clioquinol** 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 clioquinol as a single agent active ingredient, or as on... != Combination Is Not Selected

Display This Question:

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

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

- ☐ Clioquinol 1% / Coal tar solution 2% / Hydrocortisone 1% / Metronidazole 2% / Salicylic acid 2%
- ☐ Other (please describe)_____

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

_____

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

_____

Q7. Over the past 5 years, has the frequency in which you have used compounded **clioquinol** 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 **clioquinol** instead of any FDA-approved drug product?

_____

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

- Yes
- No

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

Display This Question:

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

Q10. In what practice location(s) do you stock non-patient-specific compounded **clioquinol**? 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 **clioquinol**? 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 **clioquinol**? 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 clioquinol? Please... = Convenience

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

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

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

_____

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

_____

End of Block: Clioquinol

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) _____