Summary Report

Scopolamine Hydrobromide

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

Scopolamine hydrobromide (scopolamine HBr; UNII code: 451IFR0GXB) was nominated for inclusion on the 503B Bulks List by U.S. Compounding, Thomas Dooley, and Specialty Sterile Pharmaceutical Society. It was nominated for use in patients with motion sickness, postoperative nausea and vomiting, sea sickness, and anxiety via various administration methods:

- 0.4mg/mL preserved solution for intramuscular, intravenous, and subcutaneous injection.
- 0.1-0.5mg/dose mucosal (e.g. sublingual and suppositories) and oral solids (e.g. tablets and films).

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

- Manufacturer backorder.
- The need for different strengths or dosage forms than the commercially available product.
- The need for ready-to-use packaging by a facility.
- FDA-approved product is available as transdermal patch, but physicians desire to have alternative routes of delivery.
- Physicians may desire to use in combination with other active pharmaceutical ingredients (API).
- It is relatively unsafe to expose the direct compounding area to hundreds of vials or ampules and hundreds of aseptic manipulations during the compounding of a typical batch size for an outsourcing facility; compounding from bulk is safer and more efficient.
- Commercially available finished products have an inherent variance in potency creating an uncertain final concentration for the new product.
- Use of state-of-the-art equipment, like the SKAN isolator technology, requires the use of bulk starting materials.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of scopolamine HBr 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 scopolamine HBr; name variations of scopolamine HBr 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 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing scopolamine HBr. 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 11, 2019. The search included a combination of ("scopolamine bromide"[TIAB] OR "scopolamine hydrobromide"[TIAB] OR "scopolamine hbr"[TIAB] OR "hyoscine bromide"[TIAB]) AND (injection OR intravenous OR intramuscular OR subcutaneous OR mucosal OR oral) AND ("humans"[MeSH Terms] AND English[lang]). 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

Literature reviews and/or meta-analyses, cost-effectiveness, and epidemiological studies were excluded. Articles were considered relevant based on the identification of a clinical use of scopolamine or the implementation of scopolamine 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.

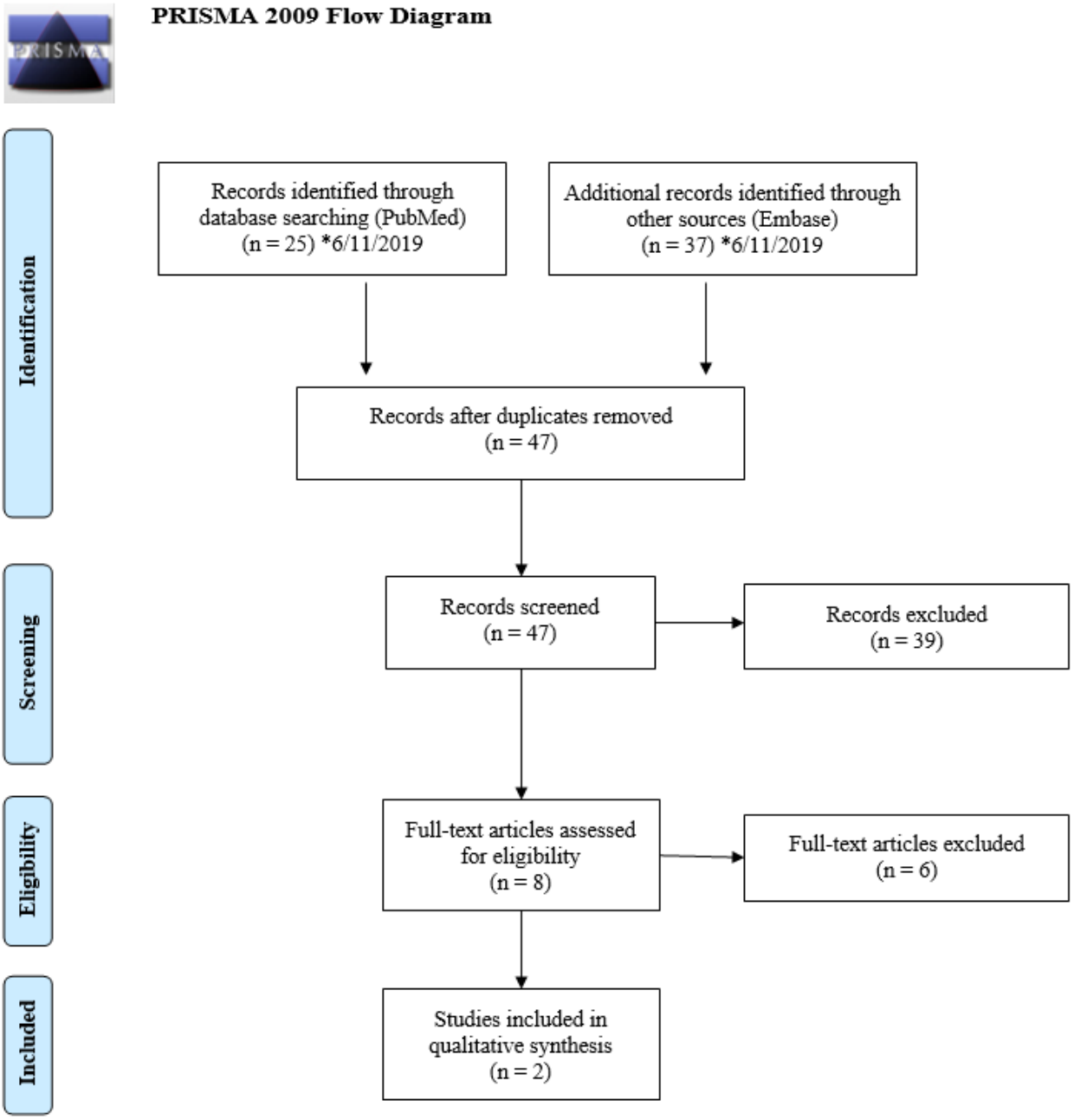
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for scopolamine 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 scopolamine 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, four (4) medical specialties that would potentially use scopolamine HBr were identified: dentistry, oral medicine, primary care, and psychiatry. 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. Two (2) experts were contacted for interviews, of which zero (0) accepted; both medical experts failed to respond to the interview request. No interviews were conducted.

Survey

General professional medical associations and specialty associations for dentistry, oral medicine, primary care, and psychiatry, identified from the nominations and literature review, 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 six (6) 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
Oral Medicine	American Academy of Oral Medicine (AAOM)
Primary Care	American Academy of Environmental Medicine (AAEM)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Dentistry	American Dental Association (ADA)	Declined, ADA concluded that this issue does not affect enough dentists to warrant a significant investment of time"
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond
Psychiatry	American Psychiatric Association (APA)	Declined, "we have put this ask to our members and unfortunately, we have not received any information on psychiatrists using compounded products"

CURRENT AND HISTORIC USE

Summary of background information

- Scopolamine HBr is not available as an FDA-approved product. Scopolamine is available as a 1mg/72 hour transdermal patch.
- Scopolamine HBr is available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for scopolamine HBr.
- Scopolamine HBr is available in Australia, Belgium, Canada, Hong Kong, Ireland, New Zealand, and UK in the nominated dosage form/ROA. In Abu Dhabi and Namibia, scopolamine HBr product is available in other dosage form/ROA.

Table 3. Currently approved products – US

No approved products in the US

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

Active Ingredient	Concentration	Dosage Form	ROA	Approved For Use		
				Country	Status	Approval Date[b]
Hyoscine HBr	0.4mg/mL	–	Injection	Hong Kong	Prescription	12/9/1978
	0.4-0.6mg/mL	Solution		Ireland	Prescription-only non-renewal	8/26/2005
	0.4-20mg/mL			New Zealand	Prescription	12/31/1969
	0.4mg/mL		Injection (intramuscular, intravenous, subcutaneous)	Australia	Schedule 4- Prescription only	10/8/1991
	0.25-0.5mg/mL			Belgium	Medical prescription	1/2/2012
	0.4-20mg/mL			UK	Prescription-only	5/10/1989
	0.15-0.3mg	Chewable tablet	Oral	Australia	Schedule 2- Pharmacy	4/6/1999
	0.15mg			UK	Pharmacy[c]	7/22/1973
	0.15mg	Tablet	–	Hong Kong	Pharmacy[c]	5/9/2016
	300mcg		Oral	Ireland	Pharmacy[c]	4/1/1979
	10-20mg			New Zealand	Prescription, restricted	12/31/1969
	0.3-10mg			UK	Pharmacy[c], prescription-only	6/10/1988
Scopolamine HBr	0.4-0.6mg/mL	Liquid	Intramuscular, intravenous, subcutaneous	Canada	Ethical	5/31/2008

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

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

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

[c]Pharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Summary of literature review

- Total number of studies included: 2 studies (2 experimental).
- No US studies were identified. The studies were from Finland and Iran (1 study each).
- The most common indications from the non-US studies were major depressive disorder and dental salivary suppression.
- No compounded products were identified from any studies.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive	0
Experimental[1,2]	2
Observational	0

Table 6. Number of studies by country

Country	Number of Studies
Finland[2]	1
Iran[1]	1
	Total US: 0 Total Non-US Countries: 2

Table 7. Number of studies by combinations

No combination product(s) were nominated

Table 8. Dosage by indication – US

No US studies included

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Major depressive disorder[1]	1mg/day	0.5mg	Tablet	Oral	6 weeks
Dental salivary suppression[2]	20mcg/kg	0.25%	Solution	Oral	Once

Abbreviation: ROA, route of administration.

Table 10. Compounded products – US

No US studies included

Table 11. Compounded products – non-US countries

No compounded products from reported studies

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

Zero (0) interviews were conducted.

Table 12. Overview of interviewee

No interviews were conducted

Summary of survey results

Table 13. Characteristics of survey respondents [9 people responded to the survey[a]]

Board Certification	DMD/DDS	No response
Oral medicine	2	0
Pain medicine	1	0
Sleep medicine	1	0
No response	0	7

Abbreviations: DMD/DDS, Doctor of Medicine in Dentistry.

[a]Some respondents reported more than one terminal clinical degree or board certification.

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

Types of Products	Respondents, n (N=2[a])
Compounded	0
FDA-approved	0
Over-the-counter	0
Dietary	0
Unsure	0
No response	2

[a]Out of 9 respondents, 2 reported using, prescribing, or recommending scopolamine HBr product.

Table 15. Compounded use of scopolamine HBr in practice

No survey respondents provided this information

Table 16. Indications for which scopolamine HBr is considered a standard therapy

Indication	Standard Therapy		
	Compounded, n (N=0)	Non-compounded, n (N=0)	No Response, n (N=2)
No response	0	0	2

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 scopolamine HBr usage over the past 5 years

No survey respondents provided this information

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

No survey respondents provided this information

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

No survey respondents provided this information

CONCLUSION

Scopolamine HBr (UNII code: 451IFR0GXB) was nominated for inclusion on the 503B Bulks List by U.S. Compounding, Thomas Dooley, and Specialty Sterile Pharmaceutical Society for motion sickness, postoperative nausea and vomiting, sea sickness, and anxiety. The nominated ROA and dosage forms include a preserved solution for intramuscular, intravenous, and subcutaneous injection; mucosal and oral solids and semi-solids. Scopolamine HBr is available in Australia, Belgium, Canada, Hong Kong, Ireland, New Zealand, and UK in the nominated ROA/dosage form. In the US, it is available OTC.

From the literature review, no US studies were identified. The most common indications from the non-US studies were major depressive disorder and dental salivary suppression. No compounded products were identified from any studies.

No interviews were conducted, and from the survey responses, two (2) out of nine (9) respondents used scopolamine HBr, but none used a compounded product.

APPENDICES

Appendix 1. References

1. Khajavi D, Farokhnia M, Modabbernia A, et al. Oral scopolamine augmentation in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2012;73(11):1428-1433.
2. Markkanen YJ, Pihlajamaki K. Oral scopolamine hydrobromide solution as an antisialagogic agent in dentistry. *Oral Surgery Oral Medicine and Oral Pathology.* 1987;63(4):417-420.

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 **scopolamine HBr**. 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: Scopolamine HBr

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **scopolamine HBr**? 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 scopolamine HBr? Please check all th... != Compounded drug product

Skip To: Q2 If What type(s) of product(s) do you use, prescribe, or recommend for scopolamine HBr? Please check all th... = Compounded drug product

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Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for scopolamine HBr? Please check all th... = Compounded drug product

Q2. Please list any conditions or diseases for which you use compounded **scopolamine HBr** 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 **scopolamine HBr** 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 scopolamine HBr as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

If Loop current: Do you use compounded scopolamine HBr as a single agent active ingredient, or as one active ingredient... = Combination

Q4. Please list all combination products in which you use compounded **scopolamine HBr**.

_____

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

_____

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

_____

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

_____

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

- Yes
- No

Skip To: End of Block If Do you stock non-patient-specific compounded scopolamine HBr in your practice location? = No

Display This Question:

If Do you stock non-patient-specific compounded scopolamine HBr in your practice location? = Yes

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

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded scopolamine HBr? Please check all that apply. = Emergencies

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded scopolamine HBr? Please check all that apply. = Other (please describe)

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

_____

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

_____

End of Block: Scopolamine HBr

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