Summary Report

Cupric Sulfate

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:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

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REVIEW OF NOMINATIONS

Cupric sulfate (UNII code: LRX7AJ16DT) was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society and Rebecca Mitchell as a 0.39mg/mL, 0.4mg/mL, 1.57mg/mL, and/or 3.93mg/mL intravenous preservative-free and preserved solution for nutrition. Cupric sulfate will also be compounded as a single agent active pharmaceutical ingredient (API) and in combination with other trace elements.

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

- 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.
- Manufacturer backorders
- When a different strength or dosage form is ordered by the practitioner or when ready-to-use packaging is required by the facility.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of cupric sulfate 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 cupric sulfate; name variations of cupric sulfate 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 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 cupric sulfate. 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 ("cupric sulfate"[TIAB] OR "copper II sulfate"[TIAB] OR "copper sulfate"[TIAB] OR "blue vitriol"[TIAB]) AND (solution OR intravenous OR parenteral) 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. Cupric sulfate 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 cupric sulfate 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 cupric sulfate or the implementation of cupric sulfate 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.

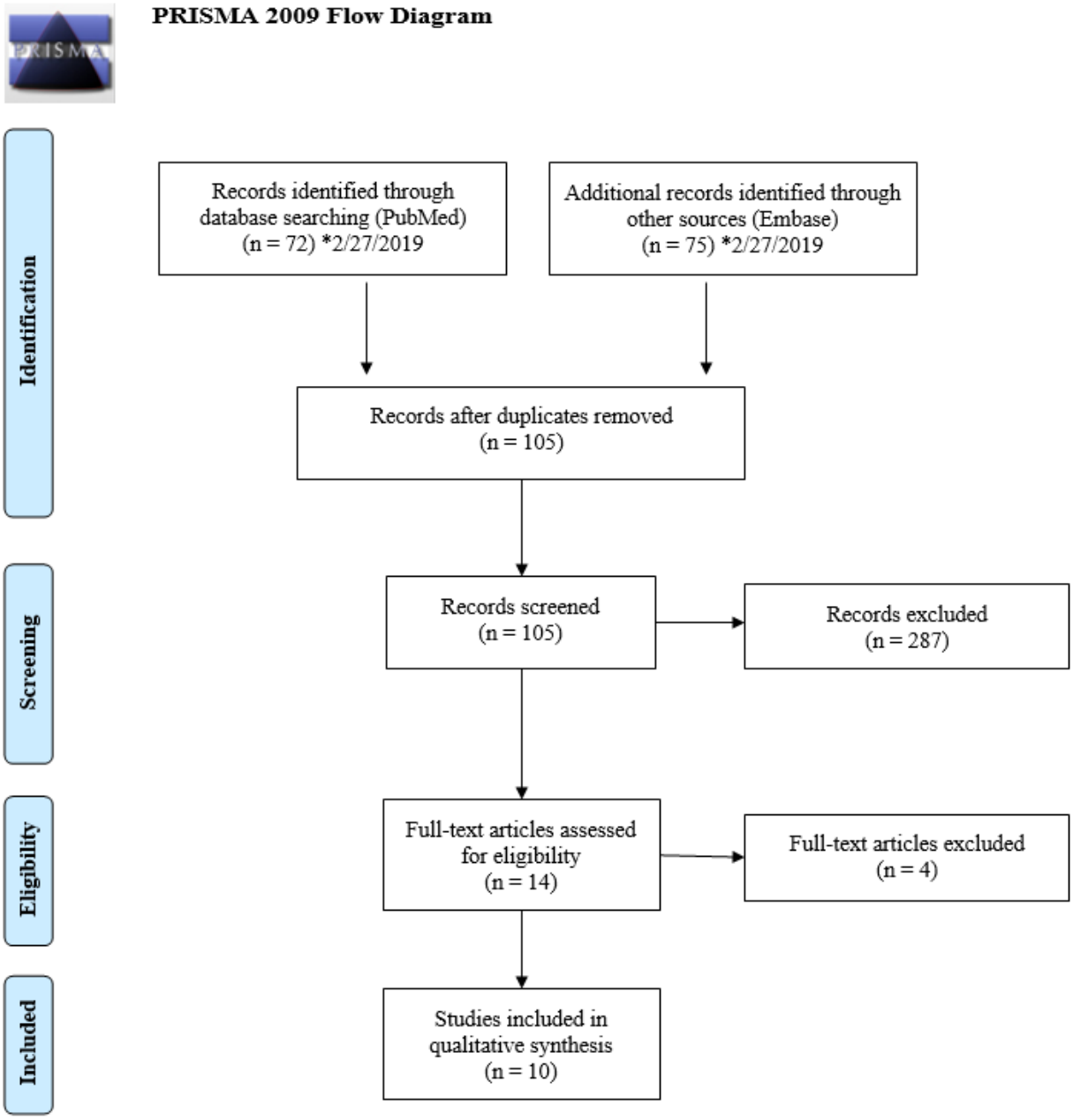
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for cupric sulfate 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 cupric sulfate 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 indication from the nominations and the results of the literature review, six (6) medical specialties that would potentially use cupric sulfate were identified: gastroenterology, naturopathy, neurology, pediatrics, primary care, and wound care. To determine if a formal interview was warranted, two (2) medical experts were provided the list of substances pertinent to their specialty via email, one is an MD specializing in gastroenterology and the other is an MD specializing in neurology. The gastroenterologist replied that they do not utilize any of the substances listed. The neurologist failed to respond to the interview request. No additional follow-up was considered necessary with this or any other experts.

Survey

General professional medical associations and specialty associations for gastroenterology, naturopathy, neurology, pediatrics, primary care, and wound care, 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 eleven (11) 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
Naturopathy	American Association of Naturopathic Physicians (AANP)
Pediatrics	American Academy of Pediatrics (AAP)
Primary Care	American Association of Environmental Medicine (AAEM)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Gastroenterology	American Gastroenterological Association (AGA)	Failed to respond
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Neurology	American Academy of Neurology (AAN)	Failed to respond
Primary Care	American College of Physicians (ACP)	Failed to respond
	American Academy of Family Physicians (AAFP)	Failed to respond
Wound Care	American Professional Wound Care Association (APWCA)	Failed to respond
	Wound Healing Society (WHS)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

- Cupric sulfate is not available as an FDA-approved product. Cupric sulfate is available as a solution for injection in combination with other trace elements as an unapproved drug in the US. These products are available under the trade names Multitrace-4 (1.57mg/mL), Multitrace-4 Concentrate (3.93mg/mL), Multitrace-4 Pediatric Concentrate (0.4mg/mL), Multitrace 4-Neonatal (0.39mg/mL), Multitrace-5 (1.57mg/mL), Multitrace-5 Concentrate (3.93mg/mL), and Trace Elements 4 (0.4mg/mL). Additionally, cupric chloride is available as an FDA-approved product.
- Cupric sulfate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for cupric sulfate.
- Cupric sulfate is not available in any of the foreign regulatory databases searched. In Latvia, cupric sulfate is available as a multiple active ingredient solution for infusion.

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 the selected non-US countries and regions

Summary of literature review

- Total number of studies included: 10 studies (8 descriptive and 2 experimental).
- Most of the studies were from the US (6 studies).
- The most common indication in the US was copper deficiency. From the non-US studies, there was not a most common indication; there was only one (1) article utilizing cupric sulfate for copper deficiency.
- No compounded products were identified from any of the included studies.

Table 5. Types of studies

Types of Studies	**Number of Studies**
Descriptive[1-8]	8
Experimental[9,10]	2
Observational	0

Table 6. Number of studies by country

Country	**Number of Studies**
India[10]	1
Israel[3]	1
Japan[7,9]	2
US[1,2,4-6,8]	6
	Total US: 6 Total non-US Countries: 4

Table 7. Number of studies by combinations

Cupric sulfate was nominated for use in combination with other trace elements; however, the specific combinations desired were not included.

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Copper deficiency[1,2,4-6,8]	1mg/week-24mg/day	1mg	Solution	Intravenous	4-9 days
	2-15mg/day	1%	Tablet	Oral	2-3 months

Abbreviation: ROA, route of administration

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Acute diarrhea[10]	5mg/day	5mg	Solution	Oral	–
Copper deficiency[9]	1000mcg/day	–	–	Enteral	28 days
Menkes kinky hair disease[7]	400mcg/kg/week	–	–	Intravenous	At least 6 months
Phosphorus burns[3]	–	1%	Solution	Irrigation	Once

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

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

No interviews were conducted. Medical experts in gastroenterology and neurology were provided the list of substances pertinent to their specialty via email, which included cupric sulfate. Per the gastroenterologist's knowledge, cupric sulfate is not used in gastroenterology. The neurologist failed to respond to the interview request.

Table 12. Overview of interviewees

No interviews were conducted

Summary of survey results

Table 13. Characteristics of survey respondents [24 people responded to the survey[a]]

Board Certification	MD	ND	PharmD	No Response
Anesthesiology	7	0	0	0
Clinical Pharmacology	1	0	0	0
Critical Care Medicine	3	0	0	0
Gastroenterology	1	0	0	0
Hospice & Palliative Medicine	1	0	0	0
Naturopathic Doctor	0	5	0	0
Naturopathic Physician	0	4	0	0
Pediatrics	5	0	0	0
Pediatric Anesthesiology	3	0	0	0
No Board Certification	0	0	1	0
No Response	0	0	0	7

Abbreviations: MD, Doctor of Medicine; ND, Naturopathic Doctor; PharmD, Doctor of Pharmacy
[a]Some respondents reported more than one terminal clinical degree or board certification.

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

No survey respondents reported using cupric sulfate

Table 15. Compounded use of cupric sulfate in practice

No survey respondents reported using cupric sulfate

Table 16. Indications for which cupric sulfate is considered a standard therapy

No survey respondents reported using cupric sulfate

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

No survey respondents reported using cupric sulfate

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

No survey respondents reported using cupric sulfate

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

No survey respondents reported using cupric sulfate

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

No survey respondents reported using cupric sulfate

CONCLUSION

Cupric sulfate (UNII code: LRX7AJ16DT) was nominated for inclusion on the 503B Bulks List as a 0.39mg/mL, 0.4mg/mL, 1.57mg/mL, and/or 3.93mg/mL intravenous preservative-free and preserved solution for nutrition. Cupric sulfate will also be compounded as a single agent active pharmaceutical ingredient (API) and in combination with other trace elements. Cupric sulfate is not available as an FDA-approved or OTC product in the US. Cupric sulfate is available as a solution for injection in combination with other trace elements as an unapproved drug in the US. Additionally, cupric chloride is available as an FDA-approved product. Cupric sulfate is not available in any of the foreign regulatory databases searched. From the literature review conducted, the most common indication in the US is copper deficiency. From the non-US studies, there was not a most common indication and there was only one (1) article for copper deficiency. No compounded products were identified from any studies. No interviews were conducted. The gastroenterologist stated that cupric sulfate is not used in gastroenterology and the neurologist failed to respond to the interview request. From the survey, zero (0) out of 24 respondents use cupric sulfate.

APPENDICES

Appendix 1. References

1. Buchman AL, Keen CL, Vinters H V, et al. Copper deficiency secondary to a copper transport defect: a new copper metabolic disturbance. *Metabolism*. 1994;43(12):1462-1469.
2. Igic PG, Lee E, Harper W, Roach KW. Toxic effects associated with consumption of zinc. *Mayo Clin Proc*. 2002;77(7):713-716.
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4. Kumar A, Jazieh AR. Case report of sideroblastic anemia caused by ingestion of coins. *Am J Hematol*. 2001;66(2):126-129.
5. Sheth S, Elnicki M. Copper deficient myeloneuropathy in celiac disease. *J Gen Intern Med*. 2014;29(Suppl 1):S338.
6. Spiegel JE, Willenbucher RF. Rapid development of severe copper deficiency in a patient with Crohn's disease receiving parenteral nutrition. *J Parenter Enter Nutr*. 1999;23(3):169-172.
7. Watanabe I, Watanabe Y, Motomura E, Nishimura M, Yazaki M. Menkes' kinky hair disease: clinical and experimental study. *Doc Ophthalmol*. 1985;60(2):173-181.
8. Zidar BL, Shadduck RK, Zeigler Z, Winkelstein A. Observations on the anemia and neutropenia of human copper deficiency. *Am J Hematol*. 1977;3(2):177-185.
9. Chen CC, Takeshima F, Miyazaki T, et al. Clinicopathological analysis of hematological disorders in tube-fed patients with copper deficiency. *Intern Med*. 2007;46(12):839-844.
10. Patel AB, Dhande LA, Rawat MS. Therapeutic evaluation of zinc and copper supplementation in acute diarrhea in children: double blind randomized trial. *Indian Pediatr*. 2005;42(5):433-442.

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 **cupric sulfate**. 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: Cupric sulfate

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? 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: Q14 If What type(s) of product(s) do you use, prescribe, or recommend for cupric sulfate? Please check all th... != Compounded drug product

Skip To: Q3 If What type(s) of product(s) do you use, prescribe, or recommend for cupric sulfate? Please check all th... = Compounded drug product

Display This Question:

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

Q2. Please list any conditions or diseases for which you use compounded **cupric sulfate** 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 **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- ☐ Single
- ☐ Combination

Skip To: Q6 If Do you use compounded cupric sulfate as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

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

Q4. Please list all combination products in which you use compounded **cupric sulfate**.

_____

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

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

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

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

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

_____

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

- o Yes
- o No

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

Display This Question:

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

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

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

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

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

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

End of Block: cupric sulfate

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