Summary Report

Tetracycline hydrochloride

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 5U01FD005946

Prepared by:

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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
AAO	American Academy of Ophthalmology
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GON	Gonococcal ophthalmia neonatorum
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of tetracycline hydrochloride (tetracycline HCl; UNII code: P6R62377KV), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how tetracycline HCl is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how tetracycline HCl has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of tetracycline HCl and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

Tetracycline HCl was nominated for inclusion on the 503B Bulks List by Fagron. Tetracycline HCl was nominated for prophylaxis of gonococcal ophthalmia neonatorum (GON) via a 1% ophthalmic ointment.

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

Reasons provided for nomination to the 503B Bulks List included that tetracycline eye ointment is not currently available in the US and other prophylactic regimens are associated with side effects.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of tetracycline HCl 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 tetracycline HCl; name variations of tetracycline HCl were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing

tetracycline HCl. 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

Tetracycline HCl is a component of an FDA-approved ophthalmic product that has been discontinued by the manufacturer, not for safety or efficacy reasons. The desired compounded product identified in the nomination did not substantially differ from the commercially available product. Therefore, a systematic literature review was not completed.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances tetracycline HCl used in a clinical setting. The systematic literature review and indication from the nomination were reviewed to identify the following medical specialties that would potentially use tetracycline HCl: ophthalmology and pediatrics and neonatology. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of tetracycline HCl in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Tetracycline HCl is not currently available as an FDA-approved product in the nominated dosage form and ROA. Tetracycline HCl was available as an FDA-approved 1% ophthalmic ointment and suspension/drops; these products have been discontinued.
- Tetracycline HCl is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for tetracycline HCl.
- Tetracycline HCl is available in the nominated dosage form and ROA in Abu Dhabi, Hong Kong, Latvia, and Saudi Arabia.

Table 1. Currently approved products – US

No approved products in the US

Table 2. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date
Tetracycline	1-3%	Ointment	–	Abu Dhabi	Active	–
	1%		Ocular	Saudi Arabia	Prescription	–
Tetracycline HCl	3%		–	Latvia	Prescription	7/5/2000
				Hong Kong	Prescription	–

Abbreviation: "– ", not mentioned.

[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. See Methodology for full explanation.

Results of literature review

No literature review was conducted.

Pharmacology and historical use

Three studies were identified that provided valuable information about the pharmacology and historical use of tetracycline HCl.

Ophthalmia neonatorum is a "conjunctivitis occurring within the first four weeks of life." [9] Ophthalmia neonatorum due to *Neisseria gonorrhoeae* (also referred to as gonococcal ophthalmia neonatorum) is transmitted intrapartum from infected mothers to their newborns. GON can lead to corneal scarring, ocular perforation, and blindness.[10] While rare in the US (0.4 cases or fewer per 100,000 live births per year), prevention is important as transmission rates of the infection from mother to newborn are between 30-50.[10,11]

In 1979, the Centers for Disease Control and Prevention (CDC) recommended a 1% silver nitrate solution, 1% tetracycline ointment, or 0.5% erythromycin ointment as effective and acceptable regimens for prophylaxis of GON, given shortly after birth.[12] The 2011 US Preventive Services Task Force statement also recommended these prophylactic regimens, stating that all three were considered equally effective.[13] However, erythromycin 0.5% is the only product currently approved by the FDA; silver nitrate solution and ophthalmic tetracycline are no longer available in the US.[13] The 2019 US Preventive Services Task Force recommendation statement on ocular prophylaxis for GON reaffirmed the 2011 recommendation statement, again stating that prophylactic ocular topical medication is recommended for all newborns to prevent GON, and 0.5% erythromycin ophthalmic ointment remains the only FDA-approved drug for this purpose.[10]

One retrospective US study was found in which the authors reviewed the charts of neonates who had received a diagnosis of conjunctivitis or ophthalmia neonatorum at their hospital over a 10-year period.[9] The authors reported that since 1952, all live-born infants at their hospital had received 50,000 units of penicillin intramuscularly for ophthalmia neonatorum prophylaxis. In 1982, 1% topical tetracycline ointment was added to this prophylaxis protocol.[9] No cases of GON had been reported since topical tetracycline and intramuscular penicillin had been administered for prophylaxis.[9]

Table 3. Types of studies

No literature review was conducted

Table 4. Number of studies by country

No literature review was conducted

Table 5. Summary of included studies

No literature review was conducted

Table 6. Dosage by indication – US

No literature review was conducted

Table 7. Dosage by indication – non-US countries

No literature review was conducted

Table 8. Number of studies by combinations

No combination products were nominated

Table 9. Compounded products – US

No literature review was conducted

Table 10. Compounded products – non-US countries

No literature review was conducted

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Three SMEs discussed tetracycline HCl. Amongst these 3 SMEs, there were 2 medical doctors and 1 certified nurse midwife. The SMEs specialized and/or were board-certified in midwifery, pediatrics and neonatology, and primary care and family medicine, working in academic medical practice. The SMEs had been in practice for 16 to 34 years.

According to one SME, there were high rates of chlamydia and gonorrhea infections in pregnant women in the late 1800s. The transmission of infection to the newborn was identified as one of the primary causes of children going blind at birth and in early childhood. In 1881, a German obstetrician started the practice of applying silver nitrate to the eyes of newborns to kill bacteria, and the number of children enrolled in blind schools decreased dramatically. However, newborns reacted to the highly caustic silver nitrate, so antibiotics, including tetracycline and erythromycin, became the safer solution.

None of the SMEs used tetracycline ophthalmic ointment as a preventative antibiotic, as it is unavailable and there are better options. One SME said that for prophylaxis of GON they primarily use erythromycin. Tetracycline can be used but there is no need for it since erythromycin has been used for a long time and is safe and effective. When asked if erythromycin allergy can be a reason why tetracycline would be used instead, an SME stated that erythromycin allergy is not likely. Since it is applied as soon as the baby is born, they would not have been exposed to erythromycin before, and since it is applied to the eye, there is no systemic absorption.

One SME used commercially available erythromycin ointment on patients. The SME speculated that in areas with higher rates of gonorrhea, there might be more need for compounded formulations. They noted that presently, the hospital provides erythromycin when a baby is born, or the SME purchases a commercially available 1-dose package for home births. The ophthalmic ointment is given to newborns

at the hospital, the birth center, or at the patient's home, depending on where labor and delivery takes place.

One SME who specialized in obstetrics and gynecology in Canada noted that chlamydia is more common than gonorrhea in the United States and Canada. Erythromycin is the better treatment for chlamydial infections, so this has become the standard antibiotic for ophthalmic prophylaxis in newborns. The SME said that tetracycline was used previously, but was discontinued in both Canada and the US, though they are uncertain about the reasons. Since the efficacy is similar between erythromycin and tetracycline, this SME stated that if tetracycline is being used, then it is more likely to be in low-resource settings where rates of gonorrhea are higher, such as Africa or China. In Canada currently, screening for these infections is part of the routine prenatal care, and patients are treated in pregnancy so they would not have these infections at the time of delivery. The same approach is taken in European countries as well. The SME was not aware of anyone using tetracycline and was unfamiliar with anyone compounding the ophthalmic ointment for this purpose.

Exposure to chlamydia and gonorrhea at birth can lead to additional infections. Gonorrheal infections are more virulent and have broad impacts if left untreated whereas chlamydial infections progress more slowly so infection may not be recognized as quickly. A challenge with using ophthalmic prophylaxis at birth, and not treating the infection antenatally, is that the baby may end up with a systemic infection if not diagnosed early. A more effective approach would be to focus on identifying and treating the infections antenatally preventing transmission entirely. One SME stated that access to healthcare may be a driving force behind the use of preventative antibiotics. The SME said that in Canada there is universal healthcare, so it is easier to get antenatal care for the mother to be screened for infection, and that most newborns are assessed within the first week of birth. Since most eye infections are due to chlamydia, and chlamydial infections progress slowly, the risk to the baby is low decreasing the need for preventative antibiotics at birth.

While an SME agreed with the recommendations of the US Preventive Task Force, they suggested looking at potential alternatives to antibiotics to reduce the risk of antibiotic resistance. The SME referenced reports about gonococcal strains found in testing as well as concerns about antibiotic resistance, suggesting that a study of prevalent strains of gonorrhea in the US, and their susceptibility or resistance to tetracycline, might be a next step in determining whether tetracycline could be beneficial.

Results of survey

Zero people responded to the survey distributed via professional medical associations and available on the project website.

A separate survey was distributed by the American Academy of Ophthalmology (AAO); 30 people responded to this survey (refer to Table 11 for respondent characteristics and to Appendix 2.2 for survey instrument).

Among respondents, 8 (16% of 50 responses, where respondents were allowed to select multiple substances) used tetracycline HCl. Four respondents (57% of 7 responses to this question) used tetracycline HCl as an ophthalmic ointment; 3 respondents (43%) did not use tetracycline HCl as an ophthalmic ointment. Respondents used ophthalmic tetracycline HCl for GON prophylaxis (2, 67% of 3 responses to this question) and blepharitis or postoperative eyelid sutures (1, 33%), indications that were not nominated (refer to Table 12).

Respondents used compounded tetracycline HCl due to lack of commercial products in an appropriate dosage form, strength or combination (50% of 2 responses to this question), patient allergies (0%), other

patient conditions preventing use of commercial products (0%), or no commercially available products with tetracycline HCl (50%). Refer to Table 13 for reasons for using compounded tetracycline HCl.

The majority of respondents (3, 75% of responses to this question) did not stock non-patient-specific compounded tetracycline HCl at their practice; 1 (25%) was not sure whether or not non-patient-specific compounded tetracycline was stocked at their practice (refer to Table 14).

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	**Responses, n (N=30)**
Doctor of Medicine (MD)	21
Doctor of Osteopathic Medicine (DO)	1
Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)	0
Nurse Practitioner (NP)	0
Physician Assistant (PA)	0
Other	0
No Response	8
Practice Setting	**Responses, n (N=30)[a]**
Physician office or private practice	16
Outpatient clinic	2
Hospital or health system	3
Academic medical center	4
Emergency room	1
Operating room	6
Compounding pharmacy	1
No response	0

[a]Some respondents reported more than one practice setting.

Table 12. Conditions for which tetracycline HCl prescribed or administered

Condition	Responses, n (N=4)[a]
Gonoccocal ophthalmic neonatorum prophylaxis	2
Blepharitis, postoperative eyelid sutures[b]	1
No Response	1

[a]Out of 30 respondents, 4 reported prescribing or using tetracycline HCl as an ophthalmic ointment.
[b]Conditions not nominated.

Table 13. Reasons for using compounded tetracycline HCl

Reason	Responses, n (N=4)[a]
Commercial product not available in desired dosage form, strength or combination	1
Patient allergies prevent use of commercial products	0
Patient conditions prevent use of commercial products	0
No commercial products	1
Other	0
No response	2

[a]Out of 30 respondents, 4 reported prescribing or using tetracycline HCl as an ophthalmic ointment.

Table 14. Use of non-patient-specific compounded tetracycline HCl

Do you stock non-patient-specific compounded tetracycline HCl at your practice?	Responses, n (N=4)[a]
Yes	0
No	3
Not sure	1
No response	0

[a]Out of 30 respondents, 4 reported prescribing or using tetracycline HCl as an ophthalmic ointment.

CONCLUSION

Tetracycline HCl was nominated for inclusion on the 503B Bulks List as ophthalmic ointment to prevent gonococcal ophthalmia neonatorum (GON). Tetracycline HCl is available in the nominated dosage form and ROA in Abu Dhabi, Hong Kong, Latvia, and Saudi Arabia.

No literature review was conducted, but the background literature indicated that 1% tetracycline ointment, 0.5% erythromycin ointment, and 1% silver nitrate solution are all equally effective for GON prophylaxis. In the US, the only FDA-approved drug is erythromycin 0.5%; the other two options are no longer available.

From the interviews conducted, SMEs stated that chlamydia and gonorrhea are the two common infections in pregnant women. Prophylactic measures were given as early as 1881 when silver nitrate was used, but it caused reactions in babies, so antibiotics were used instead. The choice of drug depends on the prevalence of chlamydia or gonorrhea in the practice area, and the availability of the recommended drugs. SMEs predominately used erythromycin, but one SME suggested that if gonorrhea is more prevalent, then prophylaxis with tetracycline might be beneficial. An SME stated that in some European countries and in Canada, they screen for infections during routine prenatal care and treat them during pregnancy, so the mothers do not have these infections at the time of delivery, eliminating the chance of transmission to the baby. An SME noted that this is possible in those countries because of universal healthcare, which makes it easy for mothers to get antenatal care.

Zero people responded to the survey distributed via professional medical associations and available on the project website. From the AAO survey responses, 8 out of 30 respondents used tetracycline HCl; 4 of the respondents who used tetracycline HCl used it as an ophthalmic ointment. The most common indication respondents used ophthalmic tetracycline HCl ointment for was GON prophylaxis. Commercial products not available in the required dosage form, strength or combination or no commercially available products containing tetracycline HCl were the reasons for using a compounded tetracycline HCl product over an FDA-approved product. Zero respondents reported stocking compounded tetracycline HCl at their practice.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

No literature review was conducted.

Appendix 2.1. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded tetracycline hydrochloride. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

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

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer tetracycline hydrochloride to your patients?

   - ○ Yes
   - ○ No

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

   - ○ Ophthalmic ointment
   - ○ None of the above

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

   - ○ Gonococcal ophthalmia neonatorum prophylaxis
   - ○ Other (please explain) _____

5. I use compounded tetracycline hydrochloride because: (check all that apply)

    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing tetracycline hydrochloride.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded tetracycline hydrochloride at your practice?

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

7. I obtain compounded tetracycline hydrochloride from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 2.2. Survey instrument for American Academy of Ophthalmology

Welcome. We want to understand your clinical use of the following compounded drugs: epinephrine; epinephrine/lidocaine combination product; flurbiprofen; tetracycline HCl. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in bulk compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

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

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Which of the following compounded drugs do you prescribe or administer to your patients? (please check all that apply)
    - ○ Epinephrine as a single agent product
    - ○ Epinephrine/lidocaine as a combination product
    - ○ Flurbiprofen
    - ○ Tetracycline
    - ○ None of the above
3. Which salt form of epinephrine do you use as a single agent product? (please check all that apply)
    - ○ Epinephrine bitartrate
    - ○ Epinephrine hydrochloride
    - ○ Unsure
    - ○ Other, please explain _____
4. Do you prescribe or administer epinephrine as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - ○ Intracameral/intraocular injection
    - ○ Ophthalmic solution
    - ○ None of the above
5. I prescribe or administer epinephrine as a single agent product for the following conditions or diseases: (please check all that apply)
    - ○ Open-angle glaucoma
    - ○ Mydriasis for intraocular surgery
    - ○ Other (please explain) _____

6. I use compounded epinephrine as a single agent product because: (please check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - Patient allergies prevent me from using commercially available products. (please explain) _____
    - Patient conditions prevent me from using commercially available products. (please explain) _____
    - There are no commercially available products containing epinephrine.
    - Other (please explain) _____
7. Do you stock non-patient-specific compounded epinephrine as a single agent product at your practice?
    - Yes
    - No
    - I'm not sure
8. I obtain compounded epinephrine as a single agent product from the following: (please check all that apply)
    - Compound myself at my practice
    - Have the product compounded by an in-house pharmacy
    - Purchase, or have a patient purchase, from a compounding pharmacy
    - Purchase, or have a patient purchase, from an outsourcing facility
    - Other (please explain) _____
9. Which salt form of epinephrine do you use in epinephrine/lidocaine combination product? (please check all that apply)
    - Epinephrine bitartrate
    - Epinephrine hydrochloride
    - Unsure
    - Other, please explain _____
10. Do you prescribe or administer epinephrine/lidocaine as a combination product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - Ophthalmic solution
    - None of the above
11. I prescribe or administer epinephrine/lidocaine as a combination product for the following conditions or diseases: (please check all that apply)
    - Local anesthetic
    - Mydriasis for intraocular surgery
    - Open-angle glaucoma
    - Other (please explain) _____
12. I use compounded epinephrine/lidocaine as a combination product because: (please check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - Patient allergies prevent me from using commercially available products. (please explain) _____

- Patient conditions prevent me from using commercially available products. (please explain) _____
- There are no commercially available products containing epinephrine/lidocaine.
- Other (please explain) _____

13. Do you stock non-patient-specific compounded epinephrine/lidocaine as a combination product at your practice?
    - Yes
    - No
    - I'm not sure
14. I obtain compounded epinephrine/lidocaine as a combination product from the following: (please check all that apply)
    - Compound myself at my practice
    - Have the product compounded by an in-house pharmacy
    - Purchase, or have a patient purchase, from a compounding pharmacy
    - Purchase, or have a patient purchase, from an outsourcing facility
    - Other (please explain) _____
15. Do you prescribe or administer flurbiprofen as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - Ophthalmic solution
    - None of the above
16. I prescribe or administer flurbiprofen as a single agent product for the following conditions or diseases: (please check all that apply)
    - Inhibition of intraoperative miosis
    - Other (please explain) _____
17. I use compounded flurbiprofen as a single agent product because: (please check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - Patient allergies prevent me from using commercially available products. (please explain) _____
    - Patient conditions prevent me from using commercially available products. (please explain) _____
    - There are no commercially available products containing flurbiprofen.
    - Other (please explain) _____
18. Do you stock non-patient-specific compounded flurbiprofen as a single agent product at your practice?
    - Yes
    - No
    - I'm not sure

19. I obtain compounded flurbiprofen as a single agent product from the following: (please check all that apply)
    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____
20. Do you prescribe or administer tetracycline as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Ophthalmic ointment
    - o None of the above
21. I prescribe or administer tetracycline as a single agent product for the following conditions or diseases: (please check all that apply)
    - o Gonococcal ophthalmia neonatorum prophylaxis
    - o Other (please explain) _____
22. I use compounded tetracycline as a single agent product because: (please check all that apply)
    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing tetracycline.
    - o Other (please explain) _____
23. Do you stock non-patient-specific compounded tetracycline as a single agent product at your practice?
    - o Yes
    - o No
    - o I'm not sure
24. I obtain compounded tetracycline as a single agent product from the following: (please check all that apply)
    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____
25. What is your practice setting? (please check all that apply)
    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please explain) _____

26. What degree do you hold? (please check all that apply)
    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please explain) _____

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations that declined in Year 1 were not contacted in Year 2.