Summary Report

Proparacaine Hydrochloride

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:

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REVIEW OF NOMINATIONS

Proparacaine hydrochloride (proparacaine HCl; UNII code: U96OL57GOY) was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society (SSPS) and Rebecca Mitchell to be used for anesthesia in eye procedures via a "0.005"-1% preservative-free and preserved ophthalmic solution. The nominators identified a need to compound in combination with other active pharmaceutical ingredients (API) for ophthalmic use; however the desired combinations were not included.

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 backorder

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of proparacaine 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 proparacaine HCl; name variations of proparacaine 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 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing proparacaine 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

Proparacaine HCl is a component of an FDA-approved product. The desired compounded products identified in the submitted nominations do not substantially differ from the commercially available product; therefore, a systematic literature review was not completed

Outreach to medical specialists and specialty organizations

Using the indication from the nominations, one (1) medical specialty that would potentially use proparacaine HCl was identified: ophthalmology. 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 ophthalmology, identified from the nominations 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
Ophthalmology	American Academy of Ophthalmology (AAO)
	American Society of Cataract and Refractive Surgery (ASCRS)
	American Society of Retina Specialist (ASRS)

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

- Proparacaine HCl is available as an FDA-approved product.
- Proparacaine HCl is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for proparacaine HCl.
- Proparacaine HCl is available in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, New Zealand, and the UK.

Table 3. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	ROA	Status	Approval Date[b]
Proparacaine HCl	0.5%	Solution/Drops	Ophthalmic	Prescription	Approved prior to 01/01/1982

Abbreviation: ROA, route of administration.
[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

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]
Proparacaine HCl[c]	5mg/mL	Eye drops	–	Abu Dhabi	Active	–
	0.5%	Eye drops, Solution	Ophthalmic	Australia	Prescription only medicine	10/15/1991
				Belgium	Medical prescription	06/19/1984
				Canada	Ethical	12/31/1971
				Hong Kong	Pharmacy-only medicine[d]	03/31/1984
				Ireland	Prescription-only renewable	03/09/2001
				Latvia	Prescription	12/15/1999
				New Zealand	Prescription	07/12/2018
				UK	Prescription-only medication	11/13/2015

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. See Methodology for full explanation.

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

[c]Proparacaine HCl used as the standard for name variations, including proxymetacaini hydrochloridum and proxymetacaine HCl.

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

Summary of literature review

No literature review was conducted.

Table 5. Types of studies

No literature review was conducted

Table 6. Number of studies by country

No literature review was conducted

Table 7. Number of studies by combinations

No literature review was conducted

Table 8. Dosage by indication – US

No literature review was conducted

Table 9. Dosage by indication – non-US countries

No literature review was conducted

Table 10. Compounded products – US

No literature review was conducted

Table 11. Compounded products – non-US countries

No literature review was conducted

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

One (1) interview was conducted.

Table 12. Overview of interviewee

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Proparacaine HCl	Interview Summary Response
OPH_05	MD	Ophthalmology Retina Specialist	Academic medical institution	Yes	• Uses proparacaine HCl for diagnostic testing. • Would not use a proparacaine HCl combination product, but can see the appeal.

Abbreviation: MD, Doctor of Medicine.

Use of proparacaine HCl

- One (1) interviewee uses proparacaine HCl to numb the eye to check eye pressure. Numbing the eye is required to do this, because otherwise the patient would not be able to tolerate the provider touching the cornea.
    - "So when you come in, we usually put an alcaine, whatever proparacaine, in your eye, check your pressure. And then your eye is numb, so that we can put the dilating drops in, which burn. So then it burns less. It only burns when you put the proparacaine in."

Use of compounded proparacaine HCl

- One (1) interviewee stated that they are fine with the current strength available (0.5%); not sure why people nominated a higher strength. The interviewee stated that they have never had a patient that the commercially available proparacaine HCl did not numb.

Proparacaine HCl as a combination product

- One (1) interviewee stated that they are fine with what they have now, and they would not personally use a combination product with proparacaine HCl, phenylephrine, and a dilating agent. They do not believe it would be less expensive than using individual products, and do not know how long it would be shelf-stable for.
    - However, they said that do see the appeal for the proparacaine HCl combination product since it would be more convenient to administer fewer drops, numbing and dilating the eye at the same time.

Summary of survey results

Table 13. Characteristics of survey respondents [95 people responded to the survey[a]]

Board Certification	MD	NP	No Response
Cardiovascular Disease	0	1	0
Internal Medicine	2	0	0
Ophthalmology	56	0	0
No Board Certification	1	0	0
No Response	0	0	37

Abbreviations: MD, Doctor of Medicine; NP, Nurse Practitioner.
[a]Some respondents reported more than one (1) board certification.

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

Types of Products	Respondents, n (N=88[a])
Compounded	4[b]
FDA-approved	52
Over-the-counter	2
Dietary	0
Unsure	2
No Response	33

[a]Out of 95 respondents, 88 reported using, prescribing, or recommending multiple types of proparacaine HCl product.
[b]Two (2) respondent reported using in combination, but no further information was provided.

Table 15. Compounded use of proparacaine HCl in practice[a]

Indication	Strength	Dosing frequency	Dosage Form	ROA	Duration of Treatment	Patient Population
To relieve pain before and after ocular surgery	–	As needed Pre-operative	Ocular drops	Ocular drops	As needed Pre-operative	Adults Cataracts
Topical anesthesia	–	–	–	Topical	In office	–

Abbreviations: "–", not mentioned; ROA, route of administration.
[a]Three (3) respondents.

Table 16. Indications for which proparacaine HCl is considered a standard therapy[a]

Indication	Standard Therapy			
	Compounded, n (N=4)	Non-compounded, n (N=49)	Unsure, n (N=2)	No Response, n (N=33)
Anesthesia for procedures[b]	2	26	1	0
Anesthesia for diagnostic testing[c]	0	24	0	0
Anterior segment trauma evaluation	0	2	0	0
Anti-VEGF treatments in-office	0	1	0	0
Intravitreal injection	0	1	0	0
Ophthalmic care	0	1	0	0
Other[d]	0	4	0	0
No Response	2	0	1	33

[a]Some respondents reported more than one indication.
[b]Includes: "any procedure requiring anesthesia of the cornea," cataract surgery, corneal debridement, foreign body removal, laser, minor procedures, pain prior to surgery, preoperative topical anesthesia, surgery
[c]Includes: anterior segment evaluation, applanation tonometry, contact tonometry, gonioscopy, intraocular pressure testing, in-office exams, retinal exam with contact lenses, routine eye exams, tear tests
[d]"Na *[sic]*," "None," "None. Used for anesthetic," "None. Only as use by health professional in the office *[sic]*."

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

Theme	Reasons
Availability	• "None available that are equivalent"
	• "To get a preservative-free product"
	• "When can't get"
Cost	• "Cheaper price"
	• "Too expensive FDA approved products from vendors"

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

	Respondents, n (N=4)
No–use has remained consistent	1
Yes–I use it LESS often now	0
Yes–I use it MORE often now • "Other meds unavailable" • "More injections into the eye"	3

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

	Respondents, n (N=4)
No	2
Yes	2

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

	Respondents, n (N=2)
In what practice locations do you stock non-patient-specific compounded proparacaine HCl?	
Physician office	1
Outpatient clinic	0
Emergency room	0
Operating room	1
Inpatient ward	0
How do you obtain your stock of non-patient-specific compounded proparacaine HCl?	
Purchase from a compounding pharmacy	2
Purchase from an outsourcing facility	0
Compound the product yourself	0
Why do you keep a stock of non-patient-specific compounded proparacaine HCl?	
Convenience	0
Emergencies	0
Other[a]	2

[a]Two (2) respondents provided alternative reasons: "Routine use," and "Essential practice medicine, and lack of access would shut down office and lead to patients going blind."

CONCLUSION

Proparacaine HCl (UNII code: U96OL57GOY) was nominated for inclusion on the 503B Bulks List for anesthesia in procedures on the eye via an ophthalmic solution. Proparacaine HCl is available as an FDA-approved product. It is also available in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, New Zealand, and the UK.

Because proparacaine HCl is a component of an FDA-approved product and the desired compounded products nominated do not significantly differ from the commercial product, a systematic review was not completed.

The interviewee reported using proparacaine HCl in practice for diagnostic testing. They commented that they have no issue with the commercially available product. The interviewee would not use proparacaine HCl as a combination product, but can see the advantage in administering fewer drops, and does not see a reason why it should not be available.

From the survey responses, 88 out of 95 respondents reported using, prescribing, or recommending multiple types proparacaine HCl products. Only two (2) of the four (4) respondents who reported using compounded proparacaine HCl gave the indication, which is anesthesia for a procedure. The most common indications that respondents used non-compounded proparacaine HCl for were anesthesia for procedures and diagnostic testing. The reasons respondents reported using compounded proparacaine HCl over the FDA-approved product were availability and cost. Three (3) respondents stated that over the past 5 years, they use proparacaine HCl more often now; one (1) said that use has remained consistent over time. Two (2) respondents report stocking non-patient-specific compounded proparacaine HCl in the physician office and operating room; they both purchase their stock from a compounding pharmacy. The reasons for stocking non-patient specific compounded proparacaine HCl were "routine use," and "essential practice medicine, and lack of access would shut down office and lead to patients going blind."

APPENDICES

Appendix 1. References

No literature review was conducted.

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 **proparacaine HCl**. 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: Proparacaine HCl

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

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

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

Display This Question:

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

Q4. Please list all combination products in which you use compounded **proparacaine HCl**.

_____

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

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

_____

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

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

- Yes
- No

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

Display This Question:

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

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

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

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

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

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

End of Block: Proparacaine HCl

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