Summary Report

Cyclopentolate 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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REVIEW OF NOMINATIONS

Cyclopentolate hydrochloride (cyclopentolate HCl; UNII codes: 6D6X07D6BN, 0UXD5V5G6V, 736I6971TE) was nominated for inclusion on the 503B Bulks List by Triangle Compounding Pharmacy, Outsourcing Facilities Association (OFA), American Society for Cataract and Refractive Surgery (ASCRS), American Society of Retina Specialists (ASRS), American Academy of Ophthalmology (AAO), and Pine Pharmaceuticals. Cyclopentolate HCl was nominated for use in combination with additional active pharmaceutical ingredients (API), refer to Table 7 for the nominated combination formulations.

Cyclopentolate HCl was nominated for use in ophthalmic surgeries and procedures as a 0.25-1% topical ophthalmic solution and gel, cycloplegia and mydriasis induction as a 0.2-2% ophthalmic solution, and cylcoplegia for pain control in chronic uveitis as well as confirmation of toric lens placement confirmation as a 0.5-1% topical drop, spray and 0.1% intracameral injection.

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

- The dilution of multiple FDA-approved products reduces the effectiveness of the drug during the procedure. The reduction to using one (1) combination product instead of multiple separate ingredients reduces the chance of the wrong medication being used and increases productivity in pre-op staging.
- It is not possible to properly formulate the required concentration of the CTP ophthalmic solution by simply combining approved sterile products. Such would render the final solution having suboptimal concentrations of each active due to dilution.
- Patients respond differently, and the compounded drug product may be the only product to effectively treat the indication for which it is intended. Specifically, patients with corneal epithelia staining or neurotrophic keratitis where the corneal epithelium is particularly susceptible to preservative toxicity, switching to a preservative-free agent may improve corneal staining and visual acuity.
- Patient sensitivities to dyes, filler, preservatives, and other excipients contained in the commercially available product; specifically benzalkonium chloride. While the lack of published reports showing improvement is due to the extremely small number of patients involved, there is well-documented evidence for the toxic effects on the corneal epithelium of preservatives in eye drops contributing to the ocular surface disease associated with tear dysfunction.
- Manufacturer backorder.
- There are no cycloplegic agents approved for intraocular use by the FDA.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of cyclopentolate 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 cyclopentolate HCl; name variations of cyclopentolate 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 cyclopentolate 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

Search strategy

Two databases (PubMed and Embase) were searched including any date through April 4, 2019. The search included a combination of (cyclopentolate[TIAB] OR "cyclopentolate hydrochloride"[TIAB] OR "cyclopentolate hcl"[TIAB]) AND (phenylephrine[TIAB] OR moxifloxacin[TIAB] OR flurbiprofen[TIAB] OR tropicamide[TIAB] OR clinic*[TIAB] OR treat*[TIAB] OR therap*[TIAB] OR ophth*[TIAB] OR topical*[TIAB] OR mydria*[TIAB] OR cyclopeg*[TIAB] OR gel[TIAB] OR dilat*[TIAB]) 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.

Upon receipt of new nominations for substances for which a literature review had already been conducted, additional search strategies were constructed for dosage forms, ROA and/or indications that were not captured in the original searches. A medical librarian constructed comprehensive search strategies for PubMed and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: cyclopentolate HCl; substances nominated for use in combination with cyclopentolate HCl; ophthalmic administration and therapeutic use (see Appendix 1 for full search strategies). Results were limited to original research articles or conference abstracts in English language. All searches were conducted on July 22, 2019. Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence for screening.

Study selection

Literature reviews and/or meta-analyses, cost-effectiveness, and epidemiological studies were excluded. Cyclopentolate HCl is a component of an FDA-approved product, as a result, articles were excluded if cyclopentolate HCl was utilized as the FDA-approved product or in the same concentration and formulation as the FDA-approved product. Articles were considered relevant based on the identification of a clinical use of cyclopentolate HCl or the implementation of cyclopentolate HCl 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.

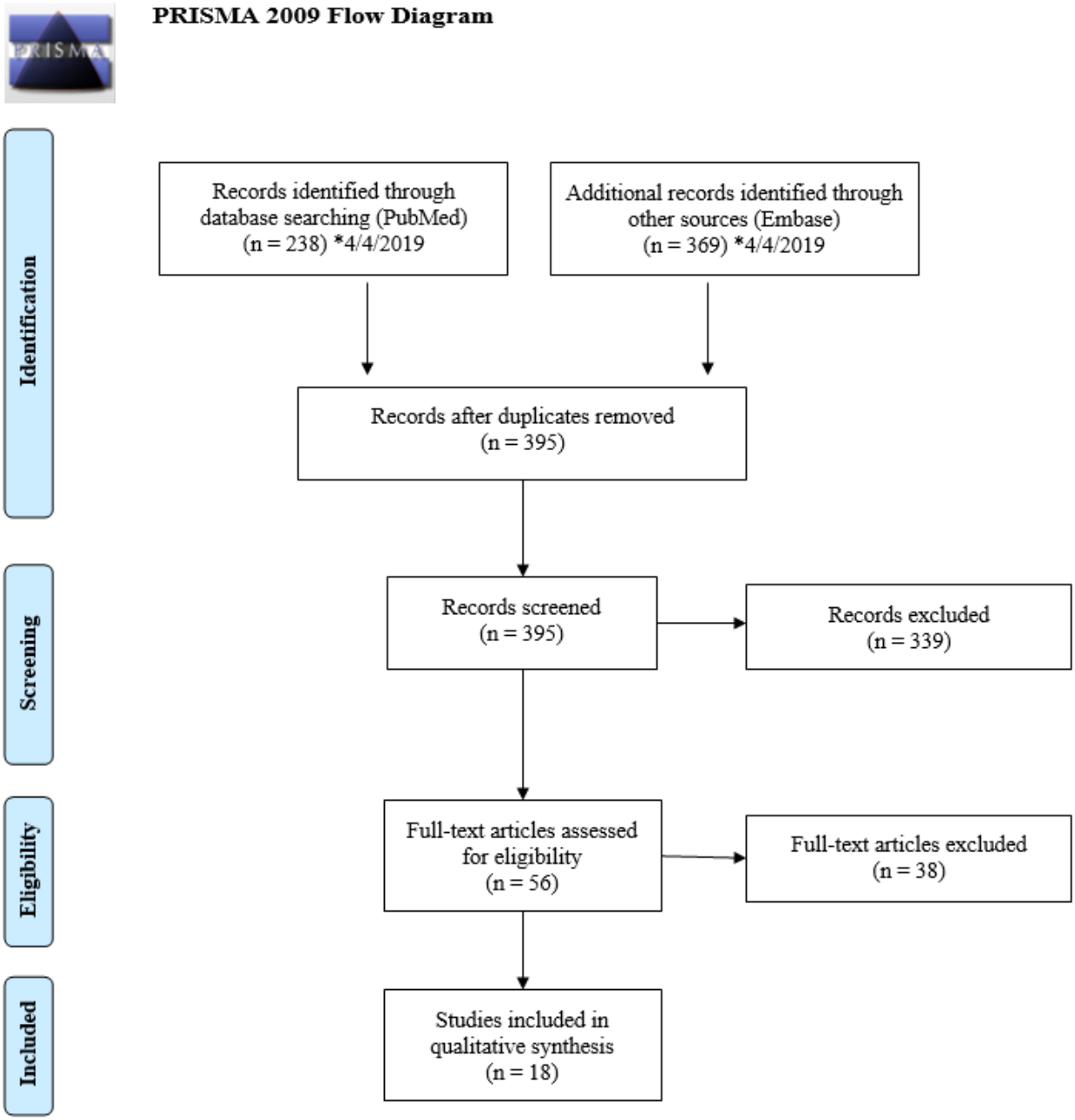
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for cyclopentolate HCl 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 cyclopentolate HCl compared to alternative therapies.

Results

Please refer to Figure 1 and Figure 2.

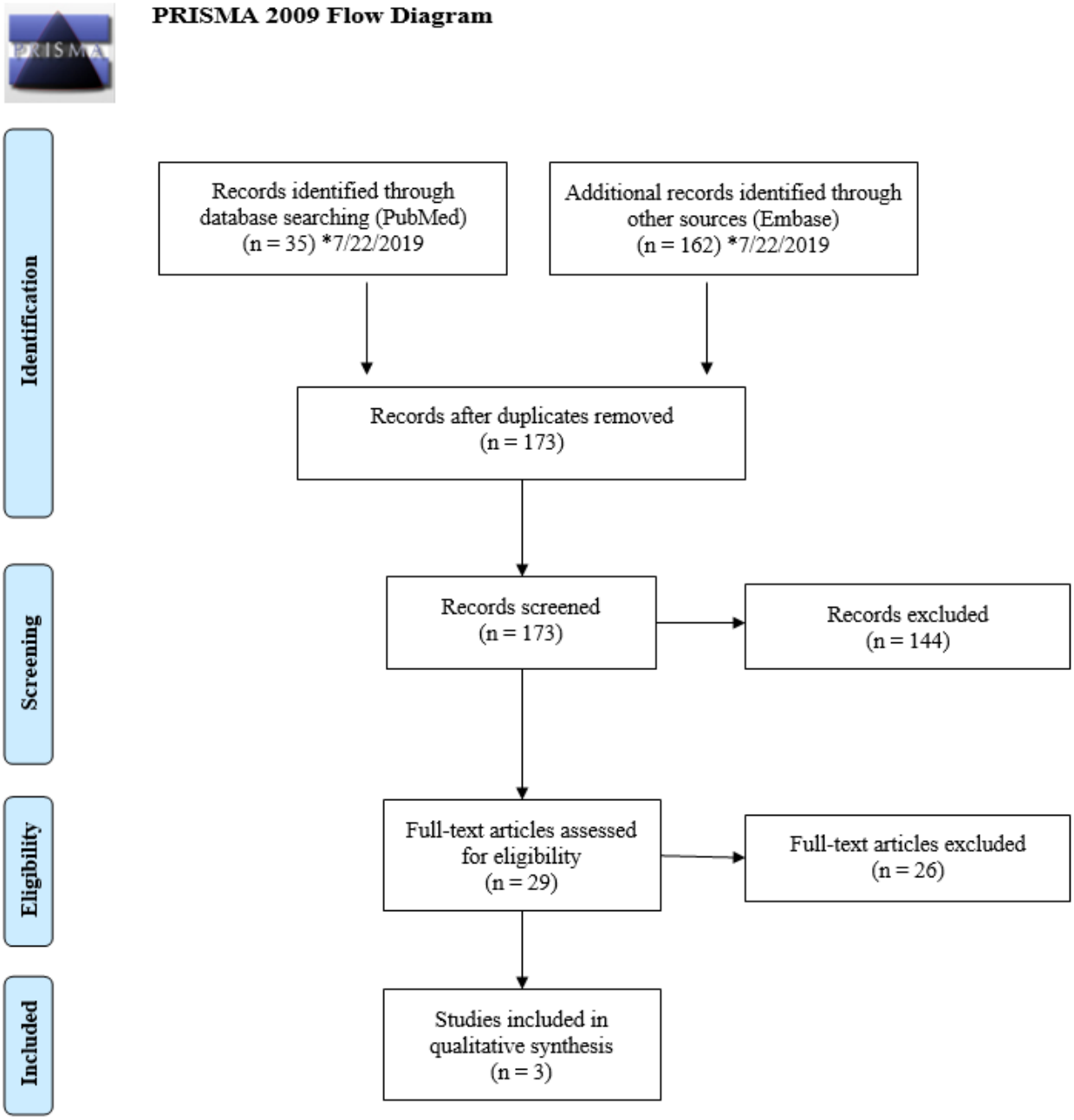
Figure 1. Summary of literature screening and selection (PRISMA 2009 Flow Diagram) - Initial Search



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.

Figure 2. Summary of literature screening and selection (PRISMA 2009 Flow Diagram) - Additional Search



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, one (1) medical specialty that would potentially use cyclopentolate 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. Two (2) experts were contacted for interviews, of which two (2) accepted and zero (0) declined. The interviews were 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, literature review, and interviews, 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 three (3) 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

No associations declined participation

CURRENT AND HISTORIC USE

Summary of background information

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

Table 3. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	ROA	Status	Approval Date[b]
Cyclopentolate HCl	0.2-2%	Solution/drops	Ophthalmic	Prescription	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]
Cyclopentolate HCl	0.1-1%	Minim, eye drops, solution	–	Abu Dhabi	Active	–
	0.05-1%	Eye drop, solution	Ophthalmic	Belgium	Prescription	10/31/1975
	0.5-1%			Australia	Prescription	10/15/1991
				Ireland	Prescription, renewable	04/01/1979
				New Zealand	Prescription	12/31/1989
				UK	Prescription	06/17/1987
	1%			Canada	Prescription	12/31/1972
				Hong Kong	Pharmacy only[c]	07/18/1979
				Latvia	Prescription	12/15/1999

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: 21 (2 descriptive, 17 experimental, and 2 observational).
- Most of the studies were from Sweden (8).
- The most common indication for use of cyclopentolate HCl in the US and non-US studies was dilation/cycloplegia.
- Compounded products were identified from both the US and non-US studies, one (1) of which was utilized in the nominated formulation.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[1,2]	2
Experimental[3-19]	17
Observational[20,21]	2

Table 6. Number of studies by country

Country	Number of Studies
Canada[14]	1
Hong Kong[17]	1
Singapore[9]	1
Spain[16]	1
Sweden[6,10-12,18-21]	8
Switzerland[7]	1
UK[4]	1
US[1-3,5,8,13,15]	7
	Total US: 7 Total non-US Countries: 14

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Cyclopentolate / Phenylephrine / Tropicamide[15-17]	3
	Cyclopentolate 1% / Fluriprofen 0.03% / Moxifloxacin 0.5% / Phenylephrine 2.5%	0
Others found in literature	Cyclopentolate 0.2%-1% / Phenylephrine 1.5%-10%[1,4-6,9,18-21]	9
	Cyclopentolate 0.5%-1% / Tropicamide 0.5%-1%[2,3,7,14]	4
	Cyclopentolate 0.1% / Phenylephrine 1.5% / Xylocaine 1%[6,10-13,21]	6

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Dilation/cycloplegia[1-3,5,8,13,15]	1 drop	0.1%-1%	Solution	Ophthalmic	1-2 applications

Abbreviations ROA, route of administration.

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Dilation/cycloplegia[4,6,7,9-12,14,16-21]	50-200mcL	0.1%-1%	Solution	Intracameral	1-4 applications
	1-3 drops			Ophthalmic	
	2 applications			Spray	

Abbreviation: ROA, route of administration.

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Dilation/cycloplegia[13]	2009	• Cyclopentolate HCl 1mg • Phenylephrine HCl 15mg • Lidocaine HCl 10mg • Sodium edetase 1mg • Boric acid 3.85mg • Aqua injectable ad 1mL	Solution	0.1%

Table 11. Compounded products – non-US countries

Indication	Compounding method	Dosage Form	Final Strength
Dilation/cycloplegia[6,10-12,17,21]	• "mixture of 0.5% cyclopentolate and 1.5% phenylephrine"	Solution	0.85%
	• Cyclopentolate HCl 1mg • Phenylephrine HCl 15mg • Lidocaine HCl 10mg • Sodium edetase 1mg • Boric acid 3.85mg • Aqua injectable ad 1mL	Solution	0.1%
	• 1% Cyclopentolate 7.5mL • 2.5% Phenylephrine 7.5mL • 1% Tropicamide 15mL	Solution	0.25%

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

Two (2) interviews were conducted.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Cyclopentolate HCl	Interview Summary Response
OPH_05	MD	Ophthalmology	Academic medical institution	Yes	• Used in the office to dilate eye. • Considered commercially available products fine for most patients.
OPH_08	MD	Ophthalmology, retina	Private	No	• Has not used.

Abbreviation: MD, Doctor of Medicine.

One interviewee reported use of cyclopentolate HCl in the office for dilation of the eye, but considers the commercially available products suitable for most patients. This interviewee stated that since the allergy to benzalkonium chloride is rare, it would not make sense to keep the compounded product in the office because it may expire prior to use. If it is necessary to obtain a preservative-free product, then prescription could be written and the patient could bring it to the office visit. The interviewee has seen people use compounded combination product with cyclopentolate HCl and neo-synephrine. The interviewee mentioned that clinicians might prefer a combination product for pediatric patients because this would reduce the number of drops needed to be administered..

Summary of survey results

Table 13. Characteristics of survey respondents [30 people responded to the survey[a]]

Board Certification	MD	NP	No Response
Cardiovascular Disease	0	1	0
Ophthalmology	17	0	0
No Board Certification	1	0	0
No Response	0	0	11

Abbreviations: MD, Doctor of Medicine; NP, Nurse Practitioner.

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

Types of Products	Respondents, n (N=29[a])
Compounded	10[b]
FDA-approved	24
Over-the-counter	1
Dietary	0
Unsure	1
No Response	1

[a]Out of 30 respondents, 29 reported using, prescribing, or recommending multiple types of cyclopentolate HCl product.
[b]Seven (7) respondent used in combination. See Figure 2 below.

Figure 2. Compounded combinations reported in the survey

Active ingredients in combination products:

- Cyclopentolate 0.5% / Ciprofloxacin 0.3% / Phenylephrine 2.5%
- Cyclopentolate HCl 0.1% / Lidocaine 1%
- Cyclopentolate HCl 1% / Phenylephrine 2.5% / Tetracaine 0.25-1%
- Cyclopentolate HCl 1-2% / Phenylephrine 2.5-5% / Tropicamide 1%
- Cyclopentolate HCl 1% / Tropicamide 1%

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

Indication	Strength	Dosing frequency	Dosage Form	ROA	Duration of Treatment	Patient Population[b]
Diagnostic dilation	1%	"Q5min x3"	Drops	Topical	Before exam	"All patients, esp kids and elderly"
Dilation prior to surgical procedure (cataract)					Day of surgery	All surgical patients
				"operative eye"	3 doses prior to surgery	Cataract surgery patients
		"Times 4"		-	-	-
Pediatric dilation	0.5%	1 drop for dilation		Both eyes	Office exam	Pediatric
Cycloplegic refraction	1%	Dilation				As indicated in clinic
Topical PF dilation	–	–	–	Topical	–	–
Intracameral injection PF dilation				Intracameral		
Eye examinations	0.5-1%	Once or twice		–		

Abbreviations: "–", not mentioned; ROA, route of administration.
[a]Five (5) respondents.
[b]Quotations are direct words from respondents.

Table 16. Indications for which cyclopentolate HCl is considered a standard therapy

Indication	Standard Therapy			
	Compounded, n (N=10)	Non-compounded, n (N=17)	Unsure, n (N=1)	No response, n (N=1)
Accommodative esotropia, strabismus	0	2	0	0
Amblyopia	0	1	0	0
Cataract surgery	1	1	0	0
Cycloplegic refraction	0	2	0	0
Diagnostic use	0	2	0	0
Dilation of pupil	1	1	0	0
Pediatric dilation	2	0	0	0
Iritis/Uveitis	0	14	1	0
Lysis posterior synechiae	0	1	0	0
Medical examination	0	1	0	0
Pre op	1	0	0	0
Post op	0	3	0	0
Other (“yes”)	1	0	0	0
No Response	5	2	0	1

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

Theme	Reasons
Availability	"Nothing approved for intracameral use" "There is no compatible FDA approved product"
Efficacy/time	"Efficacy and time to dilation" "Faster for patients pre op"
Convenience	"Less drops for patient, less drops for nurses to administer"
Preference	"I use both"

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

	Respondents, n (N=10)
No–use has remained consistent	3
Yes–I use it LESS often now	0
Yes–I use it MORE often now • "Efficacy" • "Surgery center uses it" • "Previously unavailable and we used 3 separate drops; now hospital compounds combo drop" • "It is easier and better patient care"	4
No Response	3

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

	Respondents, n (N=10)
No	3
Yes	4
No Response	3

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

	Respondents, n (N=4)
In what practice location(s) do you stock non-patient-specific compounded cyclopentolate HCl?	
Physician office	3
Outpatient clinic	3
Operating room	3
Emergency room	0
Inpatient ward	0
How do you obtain your stock of non-patient-specific compounded cyclopentolate HCl?	
Purchase from a compounding pharmacy	3
Purchase from an outsourcing facility	0
Compound the product yourself	0
Have the product compounded by an in-house pharmacy	1
Why do you keep a stock of non-patient-specific compounded cyclopentolate HCl?	
Convenience	3
Emergencies	0
Other ("all cases for dilation")	1

CONCLUSION

Cyclopentolate HCl was nominated for inclusion on the 503B Bulks List for use in ophthalmic surgeries and procedures as a 0.25-1% topical ophthalmic solution and gel, cycloplegia and mydriasis induction as a 0.2-2% ophthalmic solution, and cylcoplegia for pain control in chronic uveitis as well as confirmation of toric lens placement confirmation as a 0.5-1% topical drop, spray and 0.1% intracameral injection. Cyclopentolate HCl is approved in the nominated formulations in Abu Dhabi, Australia, Belgium, Canada, Ireland, Latvia, New Zealand, UK, and US.

From the literature review conducted, the most common indication for the use of cyclopentolate HCl in the US and non-US studies was dilation/cycloplegia. Compounded products were identified from both the US and non-US studies, one of which was utilized in the nominated formulation.

From the two interviews, one (1) interviewee used cyclopentolate HCl, but considered the commercially available products suitable for most cases. The interviewee stated that sensitivity to benzalkonium chloride is rare, and, if needed, a prescription can be written for a preservative-free product.

From the survey responses, 29 out of 30 respondents used cyclopentolate HCl. The most common indication for use of compounded cyclopentolate HCl was dilation. Availability, efficacy, and convenience were the reasons for using the compounded cyclopentolate HCl product over an FDA-approved product. Four (4) out of ten (10) respondents who used compounded products reported stocking compounded cyclopentolate HCl in the physician office, outpatient clinic, and operating room.

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APPENDICES

Appendix 1. Search strategies for new nominations

MEDLINE search strategy

- Platform: PubMed
- Years searched: 1946 to present
- Limits: Humans (search hedge); English language
- Date searched: July 22, 2019
- Number of results: 35

1	Search "cyclopentolate"[MeSH] OR cyclopentol*[tiab] OR ciclopentol*[tiab]	669
2	Search ("ciprofloxacin"[MeSH] OR "tetracaine"[MeSH] OR "ketorolac"[MeSH] OR "tromethamine"[MeSH] OR "lidocaine"[MeSH] OR ciprofloxacin*[tiab] OR tetracain*[tiab] OR amethocaine[tiab] OR dicaine[tiab] OR ketorolac*[tiab] OR tromethamine[tiab] OR trometamine[tiab] OR tromethanine[tiab] OR tromethamol[tiab] OR trometamol[tiab] OR tromethane[tiab] OR tham[tiab] OR tris[tiab] OR lidocain*[tiab] OR lignocaine[tiab])	91904
3	Search "eye"[MeSH] OR "administration, ophthalmic"[MeSH] OR "ophthalmic solutions"[MeSH] OR "injections, intraocular"[MeSH] OR "mydriasis"[MeSH] OR "uveitis, anterior"[MeSH] OR "drug combinations"[MeSH] OR "drug compounding"[MeSH] OR "therapeutic use"[subheading] OR "drug therapy"[subheading] OR "administration and dosage"[subheading] OR eye*[tiab] OR drop[tiab] OR drops[tiab] OR ophthalm*[tiab] OR ocular[tiab] OR intracameral[tiab] OR intraocular[tiab] OR inject*[tiab] OR mydria*[tiab] OR dilate*[tiab] OR dilation[tiab] OR "anterior uveitis"[tiab] OR "iridocyclitis"[tiab] OR cycloplegi*[tiab] OR "accommodation paralysis"[tiab] OR compound*[tiab]	6395325
4	Search ("animals"[MeSH] NOT "humans"[MeSH])	4601011
5	Search (#1 AND #2 AND #3)	38
6	Search (#5 NOT #4)	37
7	Search (#6 AND English[lang])	35

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Limits: Humans (search hedge); English language
- Date searched: July 22, 2019
- Number of results: 162

1	cyclopentolate'/de	1998
2	cyclopentolat*':ti,ab,tn	611
3	ciclopentolat*':ti,ab,tn	2
4	#1 OR #2 OR #3	2081
5	ciprofloxacin'/de	93544
6	ciprofloxacin$':ti,ab,tn	33726
7	tetracaine'/de	7411
8	tetracain*':ti,ab,tn	2946
9	amethocaine':ti,ab,tn	319
10	dicaine':ti,ab,tn	99
11	ketorolac'/de	9250
12	ketorolac$':ti,ab,tn	4086
13	trometamol'/de	7190
14	tromet$amine':ti,ab,tn	1338
15	tromethanine':ti,ab,tn	1
16	tromethane':ti,ab,tn	0
17	tromet$amol':ti,ab,tn	635
18	lidocaine'/de	73116
19	lidocain*':ti,ab,tn	28952
20	lignocaine':ti,ab,tn	3909
21	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	194714
22	eye drops'/de	13403

23	intraocular drug administration'/exp	10584
24	mydriasis'/de OR 'accommodation paralysis'/de	10089
25	iridocyclitis'/de	7911
26	drug formulation'/de	115535
27	drug comparison':lnk	582360
28	drop':ti,ab	105112
29	drops':ti,ab	32899
30	intracameral':ti,ab	1968
31	intraocular':ti,ab	79466
32	inject$':ti,ab	10548
33	mydria*':ti,ab	6115
34	dilate':ti,ab	4328
35	dilation':ti,ab	55569
36	anterior uveitis':ti,ab	4380
37	iridocyclitis':ti,ab	2571
38	cycloplegi*':ti,ab	3160
39	accommodation paralysis':ti,ab	22
40	compound*':ti,ab	975868
41	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	1869096
42	[animals]/lim NOT [humans]/lim	5869519
43	#4 AND #21 AND #41	172
44	#43 NOT #42	165
45	#43 NOT #42 AND [english]/lim	162

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 **cyclopentolate 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: Cyclopentolate HCl

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

Display This Question:

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

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

Display This Question:

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

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

- ☐ Cyclopentolate HCl 0.1% / Lidocaine 1%
- ☐ Cyclopentolate HCl 0.5% / Ciprofloxacin 0.3% / Phenylephrine 2.5%
- ☐ Cyclopentolate HCl 1% / Tropicamide 1%
- ☐ Cyclopentolate HCl 1% / Phenylephrine 2.5% / Tetracaine 0.25-1%
- ☐ Cyclopentolate HCl 1% / Ketorolac tromethamine 0.5% / Phenylephrine 10% / Tropicamide 1%
- ☐ Cyclopentolate HCl 1-2% / Phenylephrine 2.5-5% / Tropicamide 1%
- ☐ Other (please describe) _____

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

_____

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

_____

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

_____

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

- o Yes
- o No

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

Display This Question:

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

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

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

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

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

_____

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

_____

End of Block: Cyclopentolate 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