Summary Report

# Tropicamide

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 5U01FD005946-06

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October 2021

This report was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling $2,342,364, with 100 percent funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the U.S. Government.

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# Frequently Used Abbreviations

| | |
|---|---|
| AD | Alzheimer's disease |
| API | Active Pharmaceutical Ingredient |
| EMA | European Medicines Agency |
| EU | European Union |
| FDA | Food and Drug Administration |
| IRB | Institutional Review Board |
| NSAID | Nonsteroidal anti-inflammatory drug |
| OTC | Over-the-counter |
| PD | Parkinson's disease |
| 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 tropicamide (UNII code: N0A3Z5XTC6), 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 tropicamide 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 tropicamide 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 tropicamide 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 NOMINATIONS

Tropicamide was nominated for inclusion on the 503B Bulks List by Pine Pharmaceuticals, the Specialty Sterile Pharmaceutical Society (SSPS), and US Compounding Pharmacy. Tropicamide was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Tropicamide was nominated to induce mydriasis and cycloplegia, to decrease sialorrhea, and to diagnose Alzheimer's disease (AD) via topical ophthalmic solutions and gels, intra-oral films, ocular inserts, and intracameral injections in concentrations ranging from 0.005%-1%.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of tropicamide.

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

- There are currently no FDA-approved combinations involving tropicamide with phenylephrine and/or cyclopentolate. The combination of tropicamide and phenylephrine with or without cyclopentolate offers multiple mechanisms of action working within the eye to provide more effective mydriasis to ensure better outcomes for the patient and greater ease of use. These products have been shown, in studies, to have greater effect when in combination rather than when each eye drop is administered separately in succession. Additionally, the use of multiple drops has been shown to be time consuming (resulting in delays in the operative room), to cause systemic side effects, and to be inexact. It has been noted that when administering multiple different drops to each eye, there is confusion as to which drop has already been instilled, possibly resulting in either underdosing or overdosing of certain medications.
- There are no FDA-approved drugs to treat sialorrhea in Parkinson's disease patients. Other therapies treating sialorrhea have demonstrated effectiveness, but the side effect profiles clearly outweigh the advantages of using the drug. Tropicamide is a preferred therapy because of the ease of use/administration as well as a lack of adverse events that may lead to further complications and a decrease in compliance.
- There are no FDA-approved drugs for diagnosing AD. Tropicamide can offer an alternative more definitive method to test for this disease.
- There is no FDA-approved ocular insert for the indication of pupil dilation, and there is a proven use and clinical preference over other dosage forms.

- It is necessary to use the bulk drug substance in order to compound preservative-free formulations of these combination products. Many patients require preservative-free products and compounding with this bulk drug substances allows them to receive the treatment.
- Prescriber or hospital preference for various strengths, dosage forms, combinations with other drugs, volumes and/or final product containers for administration.
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical size batch for outsourcing facilities; a single vessel compounded from bulk API is safer and more efficient than unmanageable amounts of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100 percent potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- In order to utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.
- Manufacturer backorder.

## METHODOLOGY

*Background information*

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

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe two concepts: tropicamide, and ophthalmic, intraocular, oral or buccal administration or form (refer to Appendix 1 for full search strategies). Results were limited to human studies in English language. Searches were conducted on September 10, 2020. In addition, the ECRI Guidelines Trust® repository was searched on September 10, 2020 for clinical practice guidelines that recommended the use of tropicamide and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.3.3 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which tropicamide was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent, or treat the nominated disease or condition, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if tropicamide was used as: an FDA-approved product in the nominated dosage form, ROA, or combination; in an unspecified or non-nominated dosage form, ROA, or combination; or for an indication that was not nominated. Studies in which tropicamide was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of tropicamide; setting; total number of patients; number of patients who received tropicamide; patient population; indication for use of tropicamide; dosage form and strength; dose; ROA; frequency and duration of therapy; use of tropicamide in a combination product; use and formulation of tropicamide in a compounded product; use of tropicamide compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

*Interviews*

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances tropicamide was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify medical specialties that would potentially use tropicamide. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. 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 synthesized for qualitative data analysis.

In addition to interviews with individual SMEs, a roundtable discussion with pharmacists was held. Participants were identified through outreach to professional associations that would potentially purchase compounded products from outsourcing facilities. A prequestionnaire was distributed to those who agreed to participate to collect information about the types of facilities at which participants worked and the products they purchased from outsourcing facilities (Refer to Appendix 2 for complete survey and *Results of survey* section for results of prequestionnaire). The roundtable lasted 60 minutes and was conducted via Zoom, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

### *Survey*

A survey was distributed to the members of professional medical associations to determine the use of tropicamide 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 Years 1 and 2 were not contacted to distribute the project Year 3 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*

- Tropicamide is available as an FDA-approved product in the nominated dosage form and ROA.
- Tropicamide is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for tropicamide.
- Tropicamide is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, New Zealand, Saudi Arabia, and UK.

Table 1. Currently approved products – US[a]

| Active Ingredient | Concentration | Dosage Form | Route of Administration | Status | Approval Date[b] |
|---|---|---|---|---|---|
| Tropicamide | 0.5%, 1% | Solution | Ophthalmic | Prescription | Prior to 01/01/1982 |
| Tropicamide / Hydroxyamphetamine | 0.25% / 1% | Solution | Ophthalmic | Prescription | 01/30/1992 |

[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 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[b] |
| Tropicamide | 5 mg/mL, 10 mg/mL | Solution | Ophthalmic | Abu Dhabi | Active | – |
| | | | | Australia | Prescription only | 10/15/1991 |
| | | | | Belgium | Prescription | 09/01/1961 |
| | | | | Canada | Prescription | 12/31/1969 |
| | | | | Ireland | Prescription only | 11/01/1982 |
| | | | | New Zealand | Prescription | 12/31/1969 |
| | | | | Saudi Arabia | Prescription | – |
| | | | | UK | Prescription only | 02/05/2002 |
| Tropicamide / Phenylephrine | 0.8% / 5% | Solution | Ophthalmic | Abu Dhabi | Active | – |
| | 0.28 mg | Insert | Ophthalmic | Belgium | Prescription | 01/02/2008 |
| | | | | UK | Prescription only | 08/12/2009 |
| Tropicamide / Phenylephrine / Lidocaine | 0.2 mg/mL | Solution | Injection | Belgium | Prescription | 02/25/2016 |
| | | | | Ireland | Prescription only | 08/28/2015 |
| | | | | UK | Prescription only | 07/22/2015 |

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 like those requested in the nominations. See Methodology for full explanation.

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

*Results of literature review*

## Study selection

Database searches yielded 702 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 473 titles and abstracts were screened. After screening, the full text of 126 articles was reviewed. Seventeen articles were included; after multiple reports of the same study were merged, there were 12 included studies. One-hundred nine studies were excluded for the following reasons: wrong study design (66 studies); unspecified dosage form or ROA (23); FDA-approved dosage form, ROA, or combination (18); language other than English (1); unable to obtain full text (1).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

## Characteristics of included studies

The 12 included studies were published between 1995 and 2020. There were 12 experimental studies, 0 observational studies, 0 descriptive studies, and 0 clinical practice guidelines. The 12 studies were conducted in the following countries: Argentina, France, Italy, Poland, Portugal, Spain, UK, and US.

A total of 1429 patients participated in the 12 included studies. The number of patients in each study ranged from 18 to 591.

Outcome measures differed among the included studies and included: pupil diameter, blood pressure, heart rate, achievement of capsulorhexis without the use of any additive mydriatic treatment, patient's subjective feelings of saliva levels, saliva volume, need for antihypertensive medication, subjective iris stability, and time to maximal dilation.

Refer to Table 5 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

## Use of tropicamide

One thousand eighty-four patients received tropicamide as an experimental or comparator treatment for mydriasis, administered via the ophthalmic route in doses ranging from 3-6 drops to one insert. Duration of treatment was once. Nineteen patients received tropicamide as an experimental treatment for sialorrhea in Parkinson's disease, administered buccally in doses ranging from 0.3 mg to 3 mg.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Tropicamide was not used as a compounded product, nor was it used in a combination product (refer to Tables 8-10).

In 2 studies, the authors' concluding statement recommended the use of tropicamide for mydriasis. In 4 studies, the authors concluded that the further studies were necessary for the use of tropicamide for the treatment of sialorrhea in Parkinson's disease and mydriasis. In 6 studies, the authors' conclusions did not address the use of mydriasis. Refer to Table 5 for summary of authors' conclusions.

## Pharmacology and historical use

In addition to the 12 included studies, additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of tropicamide.

Mydriasis is the dilation of the pupil. Pupil size is controlled by the iris sphincter, which is stimulated by parasympathetic nerves, and the iris dilator, stimulated by sympathetic nerves.[6,7] In bright light the pupil constricts and in the normal adult pupil size ranges from 2-4 mm in diameter.[7] In the dark the pupil dilates and ranges from 4-8 mm in diameter.[7] Pharmacologic dilation may be necessary for certain ophthalmic procedures and examinations including dilating the pupil for examination of the fundus, to prevent posterior synechiae in uveitis, to constrict blood vessels, and to treat open-angle glaucoma.[8] The American Academy of Ophthalmology (AAO) published their revised Preferred Practice Pattern® guidelines in 2020 for comprehensive adult medical eye evaluations which outlines the components of quality ocular examinations. Part of an ocular examination should include the examination of anterior segment structures both before and after dilation.[9] The guideline continues that the evaluation of structures situated posterior to the iris is performed best through a dilated pupil.[9] The Preferred Practice Pattern® guidelines for pediatric eye evaluations states that "adequate cycloplegia is necessary for accurate retinoscopy in children because of their increased accommodative tone compared to adults."[10] The guideline states that while there is no ideal cycloplegic agent, cyclopentolate is useful and in patients with heavily pigmented irises repeating the cycloplegic drop may be needed or an adjunctive agent, like phenylephrine or tropicamide, may be useful.[10] Phenylephrine and cyclopentolate can also be used in combination to produce adequate dilation and cycloplegia.[10]

The standard method for routine pupil dilation is accomplished by using topical mydriatic eyedrops to obtain a pupil that is at least 5 mm in diameter.[6,8] As a result of the parasympathetic and sympathetic nervous system playing a role in pupil size, both sympathomimetic/adrenergic agents, like phenylephrine, and parasympathetic/anticholinergic agents, like tropicamide, can be used for mydriasis.[6,8] Sympathomimetic drugs are classified as mydriatics while anticholinergics result in both mydriasis as well as paralysis of accommodation and are classified as cycloplegics.[6,8] The ideal agent should have a rapid onset of action, provide appropriate cycloplegic effects, and have minimal side effects.[11]

Tropicamide and cyclopentolate are 2 of the most commonly used agents, with tropicamide being the preferred agent for routine dilation due to its fast onset and shortest duration of action and cyclopentolate being preferred for routine cycloplegic refraction due to its fast cycloplegia and less residual accommodation.[11] A combination of anticholinergic, sympathomimetic, and anesthetic eyedrops are generally utilized to obtain the desired level of dilation, with the combination of phenylephrine with either tropicamide or cyclopentolate being the most common regimen.[12-15] The combination of phenylephrine and tropicamide has shown to be more effective at inducing pupil dilation than either agent alone.[15-18] An anesthetic is administered to prevent the eye from tearing which can dilute the eye drops.[17,18] This regimen requires the administration of multiple drops which is time consuming and can lead to medication errors, ocular surface toxicity, and potentially cardiovascular side effects.[13,14] Additionally, only around 2-10% of the drops penetrate the anterior chamber with 80% of the instilled dose being absorbed by the conjunctiva and nasal mucosa.[12] While not available in the US, the combination of tropicamide and phenylephrine as an ophthalmic solution is available outside of the US.

Cataracts are "the leading cause of preventable visual impairment causing an estimated 43% of all cases of blindness worldwide."[19] Phacoemulsification with intraocular lens implantation is the primary surgery to remove cataracts.[19] Mydriasis is required when preforming cataract surgery because "pupil constriction increases the risk for intraoperative complications."[6] Due to challenges associated with administering multiple drops, there has been an exploration of alternative methods to administer mydriatic agents, including ophthalmic gels, ophthalmic inserts, and intracameral

injections.[6] Jinapriya et al conducted a noninferiority study evaluating the use of a multi-ingredient ophthalmic gel that contains lidocaine 1%-phenylephrine 3.4%-tropicamide 0.34%-diclofenac 0.016% compared to the standard preoperative cataract surgery pharmacologic drug protocol.[20] The multi-ingredient ophthalmic gel provided a statistically significant increase in mydriasis with no difference in corneal anesthesia compared to the standard regimen.[20] The multi-ingredient ophthalmic gel required significantly less time to administer and has the potential "to improve efficiency when preparing patients for cataract surgery without compromising pupil dilation and corneal anesthesia."[20] Moisseiev et al also compared the efficacy of an ophthalmic gel that contained tropicamide 0.5%-phenylephrine 5% to separate ophthalmic drops of tropicamide 0.5% and phenylephrine 10%.[21] The gel resulted in greater mydriasis and was associated with lower pain scores, especially in diabetic patients, and "appears to be a better alternative than the commonly used drops."[21] A 2009 stability study conducted by Bailey et al found that a compounding ophthalmic gel that contains 0.3 mL of cyclopentolate 1% ophthalmic solution, phenylephrine 10% ophthalmic solution, and tropicamide 1% ophthalmic solution in 5 mL of lidocaine 2% jelly for a final concentration of 0.51 mg/mL cyclopentolate, 5.1 mg/mL phenylephrine, and 0.51 mg/mL tropicamide was stable for 60 days in the refrigerator.[22]

Mydriasert®, an ophthalmic insert containing phenylephrine 5.38 mg and tropicamide 0.25 mg, is available widely outside of the US. A 2015 review conducted by Behndig and Korobelnik evaluated 9 studies in which Mydriasert® was compared to conventional eyedrops and found that while dilation occurred faster in patients that received the conventional eyedrops the dilation was more stable, and the maximum dilation was superior in the Mydriasert® groups.[6] Mydrane®, a preservative-free ophthalmic solution containing tropicamide 0.02%-phenylephrine 0.31%-lidocaine 1% for intracameral administration, is also available outside of the US as an alternative to the conventional mydriatic eyedrops.[13] Studies have shown that Mydrane® is an "emerging option for mydriasis/anesthesia in adults undergoing cataract surgery, with a single injection providing rapid and sustained mydriasis and generally well tolerated.[14]

Sialorrhea is the "inability to control oral secretions, resulting in excessive saliva in the oropharynx" resulting in drooling.[23] This is generally due to either neuromuscular dysfunction, hypersecretion, sensory dysfunction, or anatomic dysfunction.[24] While common in infants, sialorrhea that occurs after the age of 4 is considered pathologic.[24] Parkinson's disease (PD) is the most common cause of sialorrhea in adults effecting up to 78% of patients.[23,24] The cause of sialorrhea in PD is likely due to "impaired and infrequent swallowing, stooped posture, and a tendency for the mouth to remain open, as well as an undesired side effect of anti-parkinsonian medication" as studies have shown that saliva production is actually decreased in these patients.[25-28] Treatment is generally focused on parasympathetic tone suppression through the use of anticholinergics, adrenergic receptor agonists, or botulinum toxin.[23,25] Tropicamide is an anticholinergic drug that was formulated into an intra-oral slow dissolving film and administered to 19 PD patients in a proof-of-concept pilot study.[25] Patients received a single dose of either tropicamide 0.3 mg, 1 mg, or 3 mg or placebo.[25] Patient's subjective feeling of saliva levels and saliva volume decreased after administration of tropicamide with no reported adverse effects with the authors concluding that the antisialorrhea effects of tropicamide are "worthy of further exploration."[25] A case report of a schizophrenic patient receiving clozapine, which has a common side effect of sialorrhea, was administered 2 drops of tropicamide 1% ophthalmic solution orally with the dose increasing to 4 drops after a week.[29] Using a visual analog scale (VAS), the patient rated his sialorrhea as improving while on tropicamide.[29]

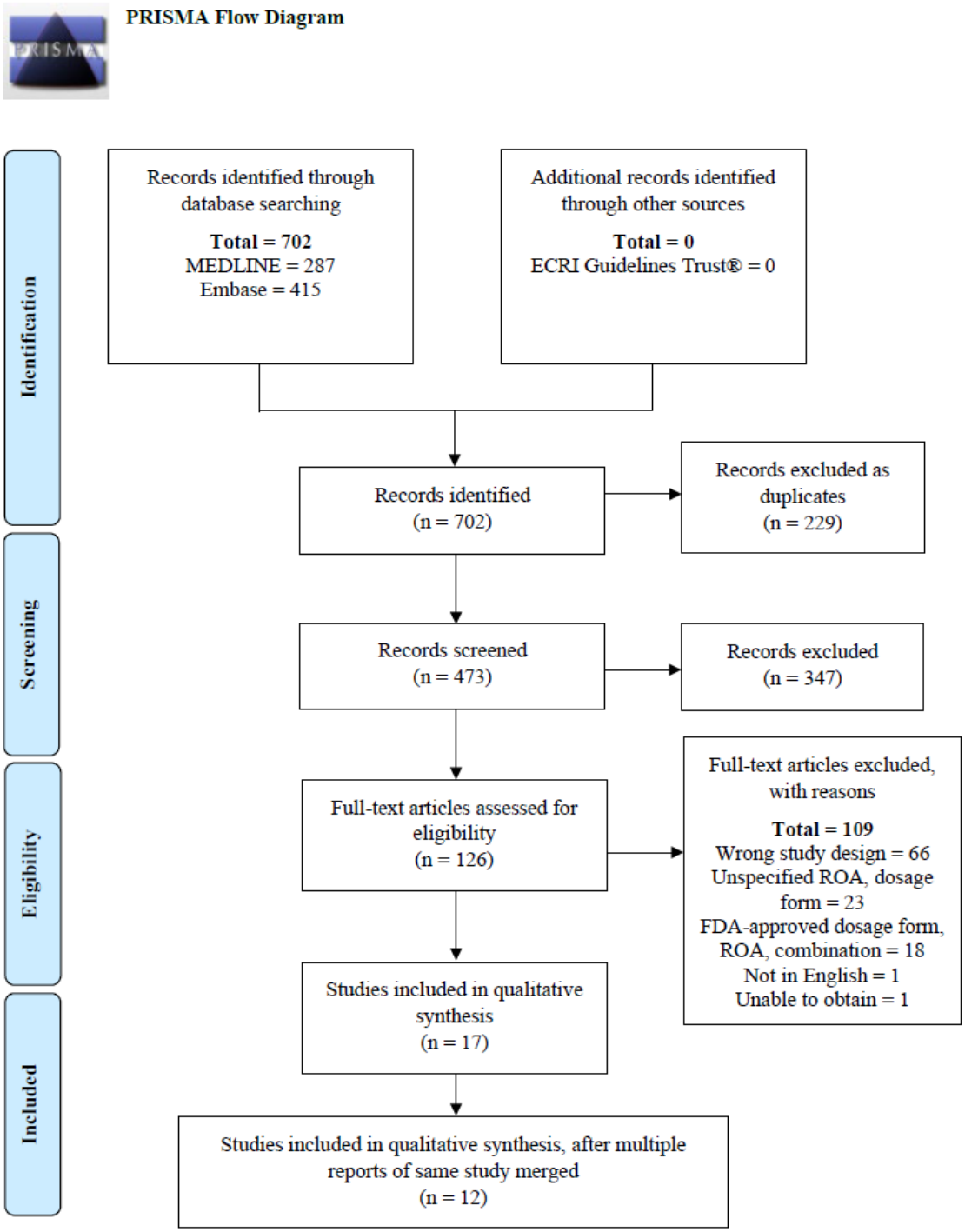
Dementia is an "overall term for a particular group of symptoms" including "difficulties with memory, language, problem-solving, and other thinking skills that affects a person's ability to

perform everyday activities."[30] There are many causes of dementia with AD being the most common cause.[30] AD is a neurodegenerative disease characterized by progressive memory loss and the decline of other higher cognitive functions.[31] Several changes to the brain are associated with AD including the accumulation of beta-amyloid plaques outside the neuron which interferes with neuron-to-neuron communication and may "contribute to the damage and death of neurons" and the accumulation of protein tau inside the neuron which "blocks the transport of nutrients and other essential molecules inside neurons."[30] The prevalence of AD increases with increasing age with approximately 6.2 million Americans over the age of 65 living with AD.[30] There is currently no single test available to diagnose AD and practitioners instead must rely on a multitude of approaches and tools to make a diagnosis.[30] In 1994, Scinto et al recognized the need for "early, noninvasive, sensitive, and easily administered diagnostic test of Alzheimer's disease."[31] By identifying a similarity in brain lesions as individuals over the age of 30 with Down syndrome the authors searched for additional physiological characteristics that may be similar in both patient groups.[31] They found that individuals with Down syndrome have a hypersensitivity to anticholinergic agents as shown by changes in heart rate or pupil size when administered these agents.[31] They administered tropicamide as an ophthalmic solution to 58 patients, 14 who had been previously diagnosed with probable AD, 4 patients with non-Alzheimer's dementia, 32 patients with no clinical signs of dementia, 5 patients with suspected AD, and 3 who had an abnormal performance on cognitive tests but no memory deficit.[31] They found that patients with probable AD "exhibited a marked hypersensitivity in their pupil dilation response" and were able to identify 18 out of the 19 patients with either diagnosed or suspected AD.[31] This was the first report of the use of tropicamide to diagnose AD.[31]

Further studies conducted to replicate the results found by Scinto et al did not come to the same conclusion. In 1997, FitzSimon et al administered tropicamide into 1 eye and placebo into the other eye to 20 patients with AD and 20 control subjects.[32] They found no difference in the mydriatic response between patients with AD and the control subjects.[32] Ferrario et al enrolled 64 patients, 20 patients with probable AD and 44 patients with no cognitive issues, to confirm the results of Scinto et al and to evaluate "the usefulness of videopupillography in the diagnosis of AD."[33] Tropicamide was administered to 1 eye and placebo to the other eye and 11 variables were measured, including pupil diameter and maximum velocity of dilation. They found no difference in pupillary response between the 2 groups concluding that "tropicamide and videopupillography do not distinguish between Alzheimer's patients and controls." [33] Graff-Radford et al also evaluate the use of tropicamide eyedrops to diagnose AD. They administered tropicamide into 1 eye and artificial tears into the other eye of 23 patients with AD, 6 with non-Alzheimer's dementia, 4 with memory difficulties, and 22 controls.[34] They found no significant difference in pupil dilation between the groups studied and concluded that "tropicamide cannot be used as a reliable diagnostic test for Alzheimer's disease."[34] Gomez-Tortosa et al "evaluated the response to dilute tropicamide solution in patients with dementia of Alzheimer type and other neurodegenerative diseases." [35] Seventy-four individuals were enrolled, 24 with AD, 7 with non-Alzheimer's dementia, 13 with extrapyramidal syndromes, and 30 controls, and they each received tropicamide in 1 eye and sterile water in the other eye.[35] They found that individuals with AD had a significantly higher maximum dilation response compared to the other groups, however, there was no distinct cut-off point identified that would allow this test to be used as a conclusive diagnostic test.[35] Litvan and FitzGibbon studied whether the pupil dilation seen after administration of tropicamide was specific to AD.[36] They evaluated 14 patients with progressive supranuclear palsy (PSP), another neurodegenerative condition that is characterized by "severe gait instability, parkinsonism not benefitting from levodopa therapy, vertical supranuclear ophthalmoplegia, pseudobulbar palsy, and mild dementia."[36] Pupil diameter was measured in 14 subjects with PSP and 14 age-matched controls after the administration of tropicamide.[36] They found

no difference in pupil diameter between the 2 groups concluding that the tropicamide pupil diameter test lacked specificity and that "physicians should be very cautious in using this test to detect AD."[36] Several other studies were conducted to replicate Scinto et al's results, and in 1998 Kardon reviewed 19 studies that included 392 patients with AD.[37] Of these 19 studies, Scinto's study was the only one to conclude that tropicamide could be a useful diagnostic test for AD leading Kardon to conclude that the tropicamide test is not clinically useful.[37] More recent studies have re-evaluated the use of tropicamide for diagnosis of AD, however, the most recent guidelines published by the National Institute of Aging does not include the use of the tropicamide eyedrop test.[38-41]

Figure 1. PRISMA flow diagram showing literature screening and selection.




Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

| **Types of Studies** | **Number of Studies** |
|---|---|
| Descriptive | 0 |
| Observational | 0 |
| Experimental[12,13,25,42-55] | 12 |
| Clinical practice guideline | 0 |

Table 4. Number of studies by country

| **Country** | **Number of Studies** |
|---|---|
| Argentina[25,50-52] | 1 |
| France[42,43,46] | 3 |
| Italy[12] | 1 |
| Poland[47] | 1 |
| Portugal[45] | 1 |
| Spain[53,54] | 2 |
| United Kingdom (UK)[48,49] | 2 |
| United States (US)[55] | 1 |
| Multi-country<br>• Algeria, Austria, Belgium, France, Germany, Italy, Portugal, Spain, Sweden[13,44] | 1 |
| | Total US: 1<br>Total Non-US Countries: 11 |

Table 5. Summary of included studies

| Author, Year, Country | Study Type[a] | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|---|---|---|---|---|---|
| **Indication 1: Mydriasis** | | | | | |
| Bremond-Gignac *et al*., 2015, France[42]<br>Bremond-Gignac *et al*., 2019, France[43] | Prospective, randomized, single-blind, non-inferiority study | 80 Infants (50%, range 1-14.9 weeks) | • Group 1: Phenylephrine and tropicamide drops (40)<br>• Group 2: Mydriasert® (40) | Pupil diameter | "The degree of mydriasis achieved with Mydriasert® was noninferior to that obtained with eye drops. The insert appears to be safe to use in neonates without a history of increased vagal tone or gastrointestinal reflux." |
| Cagini *et al*., 2014, Italy[12] | Prospective, randomized study | 77 Patients undergoing retinal angiography (64%, mean 68.7 y ± 1.9) | • Group 1: Tropicamide and phenylephrine drops (39)<br>• Group 2: Mydriasert® (38) | Pupillary dilation, blood pressure, heart rate | "Mydriasert assures an adequate degree of mydriasis for retinal angiography in both diabetic and nondiabetic patients. There are no differences in efficacy or safety between the insert and the usually administered eyedrops, but the low total drug dose administered with the insert reduces the risk of cardiovascular side effects." |
| Guell *et al*., 2019, Multi-country[44]<br>Labetoulle *et al*., 2016, Multi-country[13] | Multi-center, randomized, parallel-group study | 591 Patients undergoing phacoemulsification with intraocular lens (IOL) implantation<br>• Group 1 (40.7%, mean 69.2 y ± 9.4)<br>• Group 2 (45.3%, mean 70.6 y ± 9.2) | • Group 1: Intracameral (IC) Mydrane® (295)<br>• Group 2: Tropicamide and phenylephrine drops (296) | Achievement of capsulorhexis without use of any additive mydriatic treatment | "Mydrane is an effective and safe alternative to standard eye drops for initiating and maintaining intraoperative mydriasis and analgesia. Patients who received IC Mydrane were significantly more comfortable before IOL insertion than the reference group. Surgeons found IOL insertion less technically challenging with IC Mydrane." |

| Author, Year, Country | Study Type[a] | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|---|---|---|---|---|---|
| Morgado *et al*., 2010, Portugal[45] | Prospective, randomized study | 90 Patients undergoing phacoemulsification cataract surgery<br>• Group A (33.4%, mean 77.3 y)<br>• Group B (26.7%, mean 80.1 y)<br>• Group C (30%, mean 79.3 y) | • Group A: Tropicamide and phenylephrine drops (30)<br>• Group B: Mydriasert® (30)<br>• Group C: Intracameral lidocaine and phenylephrine (30) | Mydriasis value before ophthalmic viscoelastic device (OVD) injection and at the end of surgery, blood pressure and heart rate, need for antihypertensive medication, subjective iris stability | "The most effective mydriasis was obtained within the Mydriasert group, followed by the topical mydriasis group. From the cardiovascular point of view, intracameral mydriasis was the safest and topical mydriasis the least safe." |
| Mouly *et al*., 2006, France[46] | Phase 1, open-labeled, randomized, crossover trial | 18 Patients undergoing general clinical and ophthalmological examination (33%, range 20-36 y) | • Control phase: Phenylephrine and tropicamide drops (18)<br>• Investigational phase: Mydriasert® (18) | Pupil diameter | "Mydriasert produced similar but delayed effective and prolonged mydriasis as compared to the standard delivery system. In addition to its potential usefulness in patients undergoing cataract surgery, this delivery system may be an advantage in children who need to undergo fundus photography due to the single administration and excellent tolerance." |
| Nazim-Lipski *et al*., 2020, Poland[47] | Randomized, prospective study | 64 Patients undergoing cataract surgery<br>• Group 1 (41.4%, mean 75.4 y)<br>• Group 2 (25.7%, mean 73.6 y) | • Group 1: Mydrane® (29)<br>• Group 2: Tropicamide and phenylephrine drops (35) | Pupil diameter | "Pupil diameter was similar after drops instillation and after Mydrane injection in all patients from the Mydrane group." |

| Author, Year, Country | Study Type[a] | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|---|---|---|---|---|---|
| O'Donnell *et al*., 1995, UK[48] | Randomized controlled study | 30 Patients with insulin-independent diabetes (56.7%, range 30-71 y) | • Eye 1: Tropicamide novel ophthalmic delivery system (NODS) (not provided)<br>• Eye 2: Phenylephrine and tropicamide drops (not provided) | Pupil diameter | "We did not show any advantage of one study preparation over the other in the extent of dilation of pupils in insulin-independent diabetics. The selection of one preparation over the other when considered in terms of the difference in cost and the decreased likelihood of potential side-effects must favour the NODS preparation." |
| Patel *et al*., 1995, UK[49] | Randomized, prospective, observer-masked | 56 Patients undergoing routine extracapsular or phacoemulsification cataract extraction<br>• New regimen (33%, mean 75.7 y ± 7.5)<br>• Old regimen (35%, mean 79.3 y ± 7.4) | • New regimen: Tropicamide novel ophthalmic delivery system (NODS) and phenylephrine drops (30)<br>• Old regimen: Cyclopentolate and phenylephrine drops (26) | Horizontal pupil diameter | Tropicamide NODS is not associated with major complications and provides acceptable mydriasis in healthy eyes and less intensive preoperative mydriasis does not interfere with subjective mydriasis or the degree of surgically induced miosis. |
| Saenz-de-Viteri *et al*., 2013, Spain[53] | Two controlled, prospective, randomized, single-blind studies | Outpatient clinic study<br>• 40 Patients (40%, mean 56 y)<br>Cataract surgery study<br>• 80 Patients undergoing unilateral cataract surgery (43.75%, mean 69 y) | Outpatient clinic study<br>• Right eye: Phenylephrine and tropicamide (PT) drops (40)<br>• Left eye: Mydriasert® (MY) (40)<br>Cataract surgery study<br>• Group 1: PT drops (40)<br>• Group 2: MY (40) | Mean pupil diameter | "MY could be a safe and efficacious alternative for mydriasis. The mydriatic effect of MY is as good as conventional PT eye drops after 60 min [minutes] and is superior after 90 min [minutes]. MY also maintains good pupil dilation during cataract surgery." |

| Author, Year, Country | Study Type[a] | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|---|---|---|---|---|---|
| Torron *et al*., 2013, Spain[54] | Randomized controlled study | 70 Patients undergoing cataract surgery<br>• Group 1 (44.4%, mean 75.53 y)<br>• Group 2 (32.1%, mean 75.44 y) | • Group 1: Tropicamide, phenylephrine, and cyclopentaolate drops (35)<br>• Group 2: Mydriasert® (35) | Pupil diameter | "In summary, the effects of Mydriasert insert are comparable to those of standard mydriatic eyedrops in terms of cardiac safety and pupil dilation, and recovery of the normal pupil size fast. Therefore, Mydriasert is a good alternative option for pupillary dilation prior to cataract surgery." |
| Zoltoski *et al*., 2019, US[55] | Quantitative study | 214 Patients (gender not provided, range 30-50 y) | • Group 1: Phenylephrine 2.5%, tropicamide 0.5%, and ketorolac 0.5% gel solution<br>• Group 2: Phenylephrine 10%, tropicamide 0.5%, ketorolac 0.5% gel solution | Pupil size, maximal dilation, time to maximal dilation | "Both drug combinations were safe and effective at causing a large, stable pupil dilation. These changes in thickness and concentrations show promise for use during cataract surgery and other eye procedures. However, more analysis of age, race, and iris color is needed to determine whether a higher dose of P [phenylephrine] is needed to achieve the desired results." |
| **Indication 2: Sialorrhea in Parkinson's disease** | | | | | |
| Lloret *et al.*, 2011, Argentina[25]<br>Perez-Lloret et al., 2011, Argentina[50]<br>Perez-Lloret et al., 2011, Argentina[51]<br>Perez-Lloret et al., 2011, Argentina[52] | Double-blind, randomized, placebo-controlled, two-phased, Latin-square crossover study | 19 Patients with idiopathic Parkinson's disease (78%, mean 67 y ± 12) | • Phase A: Placebo or tropicamide 0.3 mg, 1 mg, 3 mg (12)<br>• Phase B: Placebo or tropicamide 0.3 mg, 1 mg, 3 mg (7) | • Phase A: Patient's subjective feelings of saliva levels using a visual analog scale (VAS)<br>• Phase B: Patient's subjective feelings of saliva levels using a VAS and saliva volume | Intra-oral slow dissolving films containing tropicamide are safe and exerted antisialorrhea effects worthy of further exploration. |

[a]As defined by authors.

Table 6. Dosage by indication – US

| Indication | Dose | Concentration | Dosage Form | Route of Administration | Duration of Treatment |
|---|---|---|---|---|---|
| Mydriasis[55] | 1 drop | 0.5% | Gel solution | Ophthalmic | Once |

Table 7. Dosage by indication – non-US countries

| Indication | Dose | Concentration | Dosage Form | Route of Administration | Duration of Treatment |
|---|---|---|---|---|---|
| Mydriasis[12,13,42-49,53,54] | 1-6 drops | 0.5%, 1% | Solution | Ophthalmic | Once |
| | 1 insert | 0.28 mg | Insert | Ophthalmic | |
| | 100-200 mcL | 0.02% | Solution | Intracameral | |
| | 125 mcg | 125 mcg | Film | Ophthalmic | |
| Sialorrhea in Parkinson's disease[25,50-52] | 0.3 mg, 1 mg, 3 mg | 0.3 mg, 1 mg, 3 mg | Film | Buccal | Once |

Table 8. Number of studies by combination

| | Combination Formula | Number of Studies |
|---|---|---|
| Nominated | Tropicamide / Not mentioned<br>Nomination identified the need for combination products; however, no information was provided regarding specific combinations desired | 0 |
| Others found in literature | Tropicamide / Phenylephrine / Lidocaine[13,44,47] | 2 |
| | Tropicamide / Phenylephrine[12,42,43,45,46,53,54] | 6 |

Table 9. Compounded products – US

*No compounded products from included studies*

Table 10. Compounded products – non-US countries

*No compounded products from included studies*

*Results of interviews*

One hundred eighty-four SMEs were contacted for interviews; 64 agreed to be interviewed, and 120 declined or failed to respond to the interview request. Six SMEs discussed tropicamide. The 6 SMEs were all medical doctors specializing in ophthalmology, working in academic medical institutions and outpatient practices. The SMEs had been in practice for 8 to 35 years. Additional information was collected as part of the Expanded Information Initiative, referred to as Phase 3, project in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

At the start of cataract surgery, a series of drops are applied topically to the eye that generally include an antibiotic, an anesthetic, dilating agents, and potentially a nonsteroidal anti-inflammatory drug (NSAID). The antibiotic is intended to help prevent infection, the anesthetic and NSAID decrease pain, and the dilating agents dilate the eye to increase visibility of the cataract. An SME who is a uveitis specialist stated that a challenge with cataract surgery in these patients is that "you tend to have a much higher rate of scars around the pupil" so it is important to have "the pupil well dilated to be able to visualize the cataract behind it." Compared to other dilating agents, like cyclopentolate and atropine, tropicamide does not have as long of an effect. One SME stated that cyclopentolate can last up to a day while atropine can last up to a week and while they "work well to dilate the eye" it can slow visual recovery. Since tropicamide is shorter "it lasts long enough to be effective" without slowing visual recovery.

When administering multiple drops 3-5 minutes should be allowed between each drop to minimize the dilutional effect, which often does not happen, especially in a busy preoperative area. Additionally, the eye can only hold so much volume so there is a risk that some liquid can spill out of the eye. Having a combination product available would reduce the number of drops required and allow for easier administration with one SME stating that "it is nice to have it all compounded into one delivery."

The preoperative drops used varied amongst the SMEs with one SME using a combination product that contains tropicamide, lidocaine, an NSAID, an antibiotic, phenylephrine, and cyclopentolate. Another SME does not use cyclopentolate as much and instead predominately uses tropicamide and phenylephrine. Currently, the SME does not mix them together and instead administers them as separate drops but stated it would be useful to have them together. A third SME stated that they use lidocaine gel as the anesthetic, and they prefer to use cyclopentolate over tropicamide as the dilation agent because it lasts longer than tropicamide. While another SME does not use tropicamide as a combination product, other cataract surgeons do and another SME stated, "this should be kept available as there are some legitimate uses."

Once the incision is made into the eye a combination solution containing lidocaine and epinephrine, also referred to as Shugarcaine, is injected intraoperatively into the anterior chamber of the eye. This lidocaine-epinephrine solution allows for intraoperative anesthesia as well as dilation of the eye. One SME stated that it might be advantageous to have a dilation agent in addition to the lidocaine-epinephrine

solution intraoperatively to help keep the eye dilated during surgery. Another SME stated that while epinephrine provides dilation, epinephrine only works on the sympathetic fibers of the pupil stimulating the pupil dilator muscle. Cyclopentolate and tropicamide inhibit the pupillary sphincter muscle, which is more effective for dilation. As a result, epinephrine will lead to pupil dilation, "but if you shine a light in it, it'll shrink back down" and "we've got bright lights in the eye during cataract surgery." The SME stated that during surgery "the pupil can start to shrink down a bit" continuing that "if you have something that you could do intracamerally to boost the dilation, there'd be a market for that." Another SME stated that "cataract surgeons sometimes use intracameral tropicamide, sometimes in combination with anesthetic or other dilating agents (eg, epinephrine)." However, another SME stated that the lidocaine-epinephrine solution is sufficient so there is no need for a tropicamide intraocular injection during surgery.

One SME stated that compounded products serve an important role in ophthalmology due to a lack of commercially available preservative-free products. Another SME stated that several preservatives, like benzalkonium chloride, are tertiary ammonium compounds and therefore cannot be injected into the eye due to there being a detergent effect that can damage intraocular structures. As a result, intraocular products must be preservative-free. However, with eye drops the primary risk is corneal toxicity which is more of a concern for eye drops that will be used regularly, like products used to treat glaucoma, as compared to drops that are used infrequently, like products used for dilation.

One SME mentioned the need for dilating eyedrops in uveitis, however, cyclopentolate is preferred because tropicamide is "not nearly as effective if you are trying to break high risk adhesions." However, shortages have impacted the ability to obtain cyclopentolate which may lead prescribers to have to use tropicamide or atropine which "may last too long for what you need."

Dilation also may be needed prior to retina surgery. One SME stated that they administer a drop of tropicamide and phenylephrine preoperatively, however, they have not used this as a compounded combination product. Another SME stated that they used to use intraocular tropicamide for cataract surgery to help with dilation, however, for retinal surgery the available technology allows for the surgeon to see through a mid-dilated pupil so there is not a need in retinal surgery.

As part of Phase 3, 1 nominator provided additional information the product that will be compounded using tropicamide.

Tropicamide will be compounded as a 1% ophthalmic solution for cycloplegia and mydriasis administered as a 1 time dose. This product is used by practitioners as a non-patient specific compounded product in physician offices. Tropicamide will be compounded in combination ophthalmic drops containing 2 or more active ingredients. The combination dilating drops are utilized by clinicians to achieve a strong and effective dilation and to minimize patient discomfort associated with ophthalmic procedures. The drops are used prior to retinal procedures and prior to cataract surgeries. Single agent tropicamide 1% will only be compounded in the event the commercially available product appears on the drug shortage list.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. Forty-three participants attended the event, refer to Table 15 for characteristics of the facilities that the participants represented. A prequestionnaire was also distributed to participants, refer to Tables 15-18 for results of the prequestionnaire.

While a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtain varied from less than 1% to the majority of compounded products used at one participant's facility. A participant stated "we have this method that we use where if we can buy it

commercially ready to administer, we do that. If we can't buy it in that format, then we buy it in a vial, for example, that can be snapped into a Mini-Bag Plus, because we're a Baxter house, as a second preference. If we can't buy it in either of those two formats and we can get it from a 503B, then we do that. And our last resort is compounding internally." Two participants commented that they will not outsource a product unless 2 outsourcing facilities that they contract with are able to compound the product. This redundancy will allow for a quick flip to the other outsourcing facility if there is an issue with a product compounded from one outsourcing facility, minimizing the impact to the participant's facility.

Participants were asked to discuss the decision-making process used at their facility to determine what products to obtain from an outsourcing facility. One major theme that emerged from this discussion was that many of the products purchased from outsourcing facilities are used in critical care areas, like emergency departments and operating rooms. Participants commented that outsourcing facilities are able to provide ready-to-use products that have longer beyond-use-dates compared to products compounded in-house allowing these products to be stocked in automated dispensing cabinets in these units. One participant commented that "we're always going to outsource a PCA [patient controlled analgesia] syringe because we can store it in a Pyxis machine versus us making it and storing it in a fridge." Another participant commented on the benefits of storing medications in an automated dispensing cabinet, stating that "operationally, if you have a STAT medication or something that needs to be delivered within 10 to 15 minutes, if you're looking at us doing it, you're looking at a five-minute gown and glove. If we don't have somebody in the IV [intravenous] room, if you're doing 797 right, it's five minutes. It's four minutes to tube it. It's three minutes to make it, and then you have a dosage system or a camera system, a few minutes more. We are not able to meet that need or they're just contaminating the IV room if they are trying to do it."

Having ready-to-use products available also minimizes the need for compounding and product manipulations to occur on the floor. This can be especially beneficial in children's hospitals as they face a unique need in that they are already having to perform a lot of manipulations to products due to a lack of concentrations or sizes available. One participant commented that "at baseline, already, we manipulate about 80% of what we dispense to patients" and another stated that "there's a number of drugs that require additional manipulation, to get them to a concentration that's appropriate for kids." One participant stated that "we're trying to minimize compounding, expedite actual therapies to patients in that setting [operating room], minimize manipulations as much as possible." Similarly in the emergency department, one participant stated they prefer ready-to-use products for some floor-stock items, like vasopressor infusions, to prevent compounding from occurring on the floor and another commented that "we absolutely buy as many presser drips as we can." One participant remarked that they have received requests from anesthesiologists for products that are commercially available in vials that require manipulation prior to administration to be purchased as syringes from outsourcing facilities stating that "they would prefer to have a syringe form."

Another theme regarding deciding what products to purchase from an outsourcing facility was focused on the utilization and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, like the emergency department and operating room, typically have a high product utilization and overall turnover leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency in which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented that "we look at the impact that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we're going to look to potentially move out." Another participant, while they do not obtain a lot of products from outsourcing facilities,

stated that “when we do purchase from 503B's, typically it would be if we just don't have the capacity to keep up with what the demand is.” One participant also commented that they will obtain labor intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The COVID-19 pandemic has also impacted the operations of hospitals with one participant who stated that “it's just really high volume, and the bigger the hospital, the higher the volume, especially when you have one disease state in half of your hospital” and another who expressed that “without 503B, we would’ve been in significant trouble.” One participant commented that “even though the number might be small [percent of products obtained from outsourcing facilities], some of the reasoning is quite critical, and the amount of time that it saves is very significant for beyond what we're able to do and when.“ Additionally, challenges with recruiting and retaining pharmacy technicians impact decision-making with one participant stating “it is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready to use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing.”

In addition to the evaluation of the workload on pharmacy staff, the type and capabilities of the facility also impacted the decision-making process. One participant commented that they do not have an established clean room and therefore perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use-date that can be assigned to these products and, as the participant stated, “we obviously need to provide product with much extensive beyond use dating than we can provide.” Several participants also commented that they do not perform high-risk compounding in-house and therefore, all of these products are outsourced. There are challenges with mid-size hospitals being able “to operationalize testing compounds we make for extended stability.” One participant stated, “we might make our own syringes if we could get extended dating, but I believe my operations colleagues don’t always know how to do this and adhere to the letter of the law.”

One participant also commented on the impact that The Joint Commission has had on pushing pharmacies to obtain products from outsourcing facilities. The 2018 medication management standard MM.05.01.07 was intended to move IV admixture preparation out of the nursing unit. This forced pharmacies to consider strategies to make IV admixtures available for use on the floor. Additionally, NPSG.03.04.01 states that all medications and solutions should be adequately labeled, including in operating room and other settings in which procedures are performed. USP <795> and <797> are applicable in operating room settings, stating that products should be labeled and used with one-hour, which may be problematic if syringes are drawn up at the beginning of the day and cases are canceled or delayed. The participant also commented on the cost related to purchasing premade products from manufacturers stating that “predatory pricing on premixes is present in the market.”

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products utilized. However, the products utilized in a facility are often developed in-house over decades based on physician and nurse requests, and more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, “these practices had evolved somewhat disparately, even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines.” This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said “I think we made nine different epidural concentrations, all driven by anesthesia, and they want what they want and 503Bs may not offer that. No one else in the country is buying that same concentration a 503B isn't going to go through the expense of adding that to their product list.” The participant continued that

"similar with the ADCs [automated dispensing cabinets], we've run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, 'no, we can't have it, and that's too big it won't fit,' we want it in this format and then we're stuck again because there's no 503B offering a format during that shortage that fits where it needs to go. Then we're stuck in sourcing." Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that "3% saline for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We're either going to draw that out or we're sending it to the ER with stickers all over it saying only give 150 [mL]." The participant continued that "it would be great if the FDA could look at the size of the container that they're approving and whether that's a realistic dose, is it a unit dose or isn't it."

Participants had differing opinions on the use of outsourcing facilities to obtain drugs during a shortage. Several participants stated that they will typically first restrict use of a drug on shortage, in order to conserve supply, before turning to an outsourcing facility. One participant commented that "most of the time, I will probably pursue restricting, conserving, and looking at all available options prior to going to an outsourcer on my end" and another stated, "I can only think of one time in recent history where we went to an outsourcer." One participant commented that "503Bs can't accept the additional volume if it's a true shortage. If you're not with them pre-shortage, you're not going to get products when you need it during the shortage" continuing that "typically in a shortage, you learn to live without them. You have to." Additionally, in the event of the shortage being the result of lack of an API, outsourcing facilities are likely to be equally affected and unable to provide assistance. However, one participant stated that they first began working with outsourcing facilities because of shortages. This participant commented that "what the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on API. If sterile becomes short, they quickly switch to producing through API, which ASHP [American Society of Hospital Pharmacists] and the FDA allows." This "adds a lot of flexibility so they can bounce back and forth and really try to insulate us from shortages."

A few participants commented on the use of API by outsourcing facilities. One commented that as long as they are conducting end product sterility and stability testing and the product meets quality standards, they are not concerned with the starting ingredients. As long as buyers are familiar with regulations and know what to look for, another participant commented, there should not be any issues with purchasing products compounded starting from API. Another participant stated that as more outsourcing facilities began using API, they became more comfortable with them doing so. However, one participant observed that most outsourcing facilities are switching to sterile-to-sterile and only using API if there is a shortage, stating, "I think the FDA has really looked closely at API, and they're slowly pushing the 503B outsourcers to a sterile to sterile." Only 1 participant commented that they prefer sterile-to-sterile. Another participant stated that the companies they use are all sterile-to-sterile.

A few participants commented on the need for preservative free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative containing product. So, there is a need for this product to be compounded from API as a preservative free product. One participant stated that "if there's not a preservative-free containing option, it really should be something that should be able to be compounded for bulk... especially for the pediatric patient population." However, another participant from a children's hospital stated that the need for a preservative free option has never been a reason why they have obtained a product from an outsourcing facility. Preservative free is also an issue for ophthalmic products, however, one participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they

would like to obtain from outsourcing facilities but are not able to, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products but when they reviewed the facilities, they did not pass their internal quality standards; one facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams due to the potential cross reactivity in patients with allergies. One participant stated that there are some cephalosporins they would like to obtain from an outsourcing facility but cannot because "they would have to build a separate clean room with a dedicated HVAC [heating, ventilation, and air conditioning], so you're talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn't there." Another participant stated that the concentrations required for ophthalmic antibiotics are not available but the labor and risk of compounding these products in-house is not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. LET (lidocaine-epinephrine-tetracaine) gel, for use as a topical anesthetic, was the most commonly obtained product along with buffered lidocaine to put in J-tips. Another participant stated that they obtain diclofenac suppositories from an outsourcing facility due to the high cost of indomethacin suppositories. One participant commented that most of the products they outsource are nonsterile products, generally for oral or topical administration due to a lack of commercially available products being available. The participant stated that they purchase low dose naltrexone for oral use in patients with refractory fibromyalgia and ketamine troches for patients with chronic pain. The participant continued that while the evidence does not support many of the ingredients used in topical pain products, "However, there are select patients. It's very rare that taking that cream away from them actually causes more harm than good." A few participants commented that there is a gap in the market for nonsterile products with one stating "I think that there is a large opportunity for more nonsterile products to be produced by 503Bs." Another stated that as their facility grows and acquires more outpatient clinics, they receive a lot of questions regarding obtaining products for office use. The participant noted that they often have to refer these clinics to outsourcing facilities but stated "there's not many 503Bs are doing the non-sterile for clinic use." As a result, the inpatient pharmacy is often asked to take on this role but "you don't have the space or the staff to do that."

Based on the responses to the prequestionnaire (refer to *Results of survey*), participants were asked questions regarding specific products obtained from outsourcing facilities. Several participants reported using alum (aluminum potassium) as a bladder irrigation for hemorrhagic cystitis refractory to other treatment options. Participants commented that this is high-risk compounding; they purchase alum from an outsourcing facility because they do not perform high-risk compounding in their facility. One participant commented that their policy states that high-risk compounding is not allowed except for alum. This participant wanted to move away from compounding alum in-house and stated that the addition of aluminum potassium to the bulks list might allow this to happen. Another participant had compounded alum in-house from non-sterile ingredients; however, there had been challenges with crystallization after storage. A few participants commented that there is a sterile alum powder available, which they purchase to compound in house. One participant had concerns regarding this powder, stating that "I've talked to that company, but I've had some concerns for them because they don't sell it as a drug. The owner was selling you a chemical, we're selling you a bulk API. It's just sterile. They were fuzzy and I never followed up but, when I asked about their process for verifying the sterility, as you would with a sterile product, we do USP [United States Pharmacopeia] <71> Sterility Testing. They couldn't really give me an answer. They just say they tested for sterility." The participants commented that alum is only needed a few times a year. However, as one participant observed, "when you need it, it's an emergency" and another noting that it "is a challenge for anybody who has the cyclophosphamide-induced

hemorrhagic cystitis." As a result, one participant maintains a small inventory of alum product that is purchased from an outsourcing facility but "more times than not, they go unused and expire." Another stated that they do not keep it in stock because there is a minimum purchase and there are only a few cases a year for whom they need to use alum. The participant had it STAT shipped when needed. Another participant stated that "we had a meeting with the head of urology who was baffled, why they're even ordering it. He was like, 'this is an old, really old. I don't even know why we're using it' and basically approved for us to not even make it anymore for now."

Two participants commented on the use of glycerin at their facility. One stated that they purchase it from a 503A because they were not able to find an outsourcing facility that provides this product. The participant commented that glycerin is used in 3 different concentrations at their facility, 1 for ophthalmic use, 1 for neurologic use in trigeminal neuralgia, and 1 for instilling into "a very specific kind of pump that's used to deliver a very specific kind of chemotherapy." When there are breaks in the chemotherapy regimen, the pump has to be filled with something and by using glycerin "it can go three months or something like that, so it's a huge patient satisfier to have that concentration available." The participant also commented that since they have been unable to find an outsourcing facility that compounds the concentration needed for trigeminal neuralgia, they have patients who have been waiting years for treatment. The other participant stated that they compound it in-house but said that it is not done very frequently. The participant commented that it is very difficult to sterilize due to the thickness of the product.

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution in patients undergoing dialysis with one commenting that "our nephrologists, like it in place of heparin for some patients to keep the ports patent or so they don't have to go to alteplase or some of the other drugs." There is a commercially available product; however, it is only available as a 500 mL bag and the dose needed is typically less than 30 mL. If the syringes are prepared in-house, then the beyond-use-date is limited to 12-24 hours depending on storage which results in waste.

One participant stated that they obtain papaverine from outsourcing facilities for use in urology as Bimix (papaverine/phentolamine) and Trimix (papaverine/phentolamine/alprostadil).

While none of the participants obtained sodium phosphate or aspartic acid from outsourcing facilities for use in cardioplegic solutions, a few commented that they do obtain cardioplegic solutions from outsourcing facilities. The del Nido formulation was the product most commonly obtained. One participant commented that they compound this formulation in-house because the outsourcing facilities did not offer the volume needed at their institution. Another participant commented that while they do obtain the del Nido formulation from an outsourcing facility they also compound a proprietary formulation in house. This participant observed that "it is complicated to do in-house. We do it on a, Baxa 1200 or 2,400, either one, compounder. Then we send it up to for pH and potassium testing. Obviously, then we're confined to 797 beyond-use-dates versus longer beyond-use-dates that we get from the 503B." Another participant commented that cardioplegic solutions are managed by the perfusion department, not pharmacy, and they use del Nido solution as well as 3 other formulations.

The participants also discussed challenges with utilizing outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because "it just hasn't been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to... It just isn't worth the dating that they gave us or can give us." Another commented that they obtain very little product from outsourcing facilities due to the "the amount of work for vetting and continually validating quality of these 503B outsourcing facilities." The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an

outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that "Traditionally, we've found 503B's to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed, but we've had some other smaller 503B's where we've had agreements for certain products to take it off our plate, and then low and behold they're shut down, or closed, or whatever it may be." Minimum purchase amounts were also reported as a concern with one participant stating that "what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients." Another challenge was related to outsourcing facilities utilizing API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration (DEA) places on the quantity that can be produced. The participant stated that "they [outsourcing facilities] want to buy the product that we're trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don't end up with a shortage year after year, after year and then chasing our tail. Also, we may actually want to tell 503Bs, they can't buy those products or that they're limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products, because it actually induces the shortage in many ways."

*Results of survey*

One person responded to the survey distributed via professional medical associations and available on the project website; refer to Table 11 for respondent characteristics.

Among respondents, 0 (0%) used tropicamide.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 2.2 for survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 16 for respondent characteristics. Amongst respondents, 35 (81% of 43 total respondents) utilized outsourcing facilities to obtain drug products, 4 (9%) did not utilize outsourcing facilities, and 4 (9%) did not respond to this question.

Twenty-seven respondents (19% of 143 responses, where respondents were allowed to select multiple reasons) obtained drug products from outsourcing facilities due to a need for ready-to-use products and 20 respondents (14%) obtained drug products from outsourcing facilities due to backorders (refer to Table 17).

Fourteen respondents (31% of 45 total responses, where respondents were allowed to select multiple types) obtained nonsterile products from outsourcing facilities and 31 (69%) obtained sterile products from outsourcing facilities. Refer to Table 18 for the categories of products obtained from outsourcing facilities.

Zero respondents (0% of 108 responses, where respondents were allowed to select multiple drug products) obtained tropicamide from a 503B outsourcing facility (refer to Table 19).

Table 11. Characteristics of survey respondents

*No survey respondents provided this information*

Table 12. Compounded products prescribed or administered

| Condition | Responses, n (N=1) |
|---|---|
| Acetylcysteine | 0 |
| Bupivacaine hydrochloride | 0 |
| Clonidine hydrochloride | 0 |
| Tetracaine hydrochloride | 0 |
| Triamcinolone acetonide | 1 |
| Tropicamide | 0 |
| None of the above | 0 |

Table 13. Reasons for using compounded products

*No survey respondents provided this information*

Table 14. Stock on non-patient specific compounded products

*No survey respondents provided this information*

Table 15. Obtainment of compounded topical products

*No survey respondents provided this information*

Table 16. Demographics of prequestionnaire respondents' facilities

| Type of Facility | Responses, n (N=102)[a] |
|---|---|
| Academic medical center | 15 |
| Acute care hospital | 16 |
| Children's hospital | 8 |
| Community hospital | 11 |
| Critical access hospital | 2 |
| Dialysis center | 2 |
| Federal government hospital | 4 |

| | |
|---|---|
| Health system | 15 |
| Inpatient rehabilitation center | 4 |
| Long-term acute care hospital | 3 |
| Outpatient surgery center | 6 |
| Rural hospital | 2 |
| Skilled nursing facility | 0 |
| Specialty hospital[b] | 4 |
| Trauma center | 5 |
| Urban hospital | 5 |
| **Number of Beds** | **Responses, n (N=38)** |
| < 50 | 4 |
| 50-99 | 3 |
| 100-199 | 1 |
| 200-299 | 3 |
| 300-399 | 5 |
| 400-599 | 3 |
| > 600 | 18 |

[a]Respondents allowed to select more than one type of facility.
[b]Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, oncology.

Table 17. Reasons for obtaining products from outsourcing facilities

| Categories | Responses, n (N=143)[a] |
|---|---|
| Backorders | 20 |
| Convenience | 19 |
| Cost | 10 |
| Need for concentrations not commercially available | 19 |
| Need for multi-ingredient products not commercially available | 10 |

| | |
|---|---|
| Need for preservative-free products | 3 |
| Need for ready-to-use products | 27 |
| No FDA-approved product available | 7 |
| No onsite compounding facility | 1 |
| Onsite compounding facility not equipped to compound all necessary products | 19 |
| Other[b] | 6 |

[a]Respondents allowed to select multiple categories.
[b]Respondents reported staffing shortages, need for extended dating, volume of product used, standardization projects as additional reasons for utilizing outsourcing facilities.

Table 18. Categories of products obtained from outsourcing facilities

| **Categories** | **Responses, n (N=142)[a]** |
|---|---|
| Cardioplegic solutions | 14 |
| Dermatologic preparations | 6 |
| Dialysate solutions | 0 |
| Fluids | 8 |
| Ophthalmic preparations | 10 |
| Patient-controlled analgesia | 20 |
| Ready-to-use anesthesia syringes | 25 |
| Ready-to-use antibiotic syringes and/or bags | 14 |
| Ready-to-use electrolyte solutions | 5 |
| Ready-to-use vasopressor solutions | 18 |
| Total parenteral nutrition solutions | 16 |
| Other[b] | 6 |

[a]Respondents allowed to select multiple categories.
[b]Respondents reported obtaining alum for bladder irrigation, oxytocin, anticoagulant sodium citrate solution, narcotic drips, high-cost anti-seizure medications, antiviral medications, topical pain, and oral tablets/capsules.

Table 19. Products obtained from an outsourcing facility

| Product | Responses, n (N=108)[a] |
|---|---|
| Acetylcysteine | 1 |
| Adenosine | 2 |
| Aluminum potassium sulfate | 2 |
| Aspartic acid | 0 |
| Atenolol | 0 |
| Atropine | 9 |
| Baclofen | 4 |
| Betamethasone | 0 |
| Biotin | 0 |
| Bupivacaine | 8 |
| Calcium chloride | 1 |
| Caffeine sodium benzoate | 0 |
| Cholecalciferol | 1 |
| Chromium chloride | 0 |
| Clonidine | 0 |
| Dexamethasone sodium phosphate | 0 |
| Diclofenac | 0 |
| Gentamicin | 0 |
| Glycerin | 1 |
| Hydroxyzine | 0 |
| Ketamine | 14 |
| Levocarnitine | 0 |
| Lidocaine | 8 |
| Lorazepam | 2 |
| Magnesium sulfate | 4 |

| | |
|---|---|
| Manganese chloride | 0 |
| Methylprednisolone | 0 |
| Midazolam | 15 |
| Mupirocin | 1 |
| Norepinephrine | 15 |
| Ondansetron | 0 |
| Phytonadione | 0 |
| Potassium chloride | 0 |
| Potassium phosphate | 0 |
| Prilocaine | 0 |
| Proline | 0 |
| Propranolol | 1 |
| Ropivacaine | 6 |
| Sodium chloride | 0 |
| Sodium citrate | 3 |
| Sodium phosphate | 0 |
| Tetracaine | 2 |
| Triamcinolone acetonide | 0 |
| Tropicamide | 0 |
| None of the above | 8 |

[a]Respondents were allowed to select multiple products.

## CONCLUSION

Tropicamide was nominated for inclusion on the 503B Bulks List as topical ophthalmic solutions and gels, intra-oral films, ocular inserts, and intracameral injections in concentrations ranging from 0.005%-1% to induce mydriasis and cycloplegia as well as to decrease sialorrhea, and to diagnose AD.

From the literature review tropicamide is commonly used to induce mydriasis. One study utilized tropicamide to decrease sialorrhea, however, additional studies are needed to determine the potential use. From the interviews, tropicamide is used prior to cataract and retina surgery. Several drops must be administered prior to surgery and the eye is limited in the volume it can hold so there is a potential benefit to having a compounded multi-ingredient product available. Some SMEs could see a use for intracameral tropicamide, however, others commented that the lidocaine-epinephrine mixture that is commonly used is sufficient. As part of Phase 3, 1 nominator provided additional information the product that will be compounded using tropicamide. Tropicamide will be compounded as a 1% ophthalmic solution in combination with additional APIs to achieve a strong and effective dilation and to minimize patient discomfort associated with ophthalmic procedures. A single agent product will only be compounded in the event the commercially available product appears on the drug shortage list.

From the survey responses, 0 out of 1 respondent used tropicamide. From the prequestionnaire, 0 respondents obtained tropicamide from a 503B outsourcing facility.

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## APPENDICES

*Appendix 1. Search strategies for bibliographic databases*

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to September 9, 2020
- Date last searched: September 10, 2020
- Limits: Humans (search hedge); English language
- Number of results: 287

| | | |
|---|---|---|
| 1 | tropicamide/ | 601 |
| 2 | tropa acid amid$.tw. | 0 |
| 3 | tropicacyl.tw. | 2 |
| 4 | tropi#amid$.tw. | 821 |
| 5 | or/1-4 | 1013 |
| 6 | exp administration, oral/ | 146659 |
| 7 | administration, ophthalmic/ | 1241 |
| 8 | exp injections, intraocular/ | 7917 |
| 9 | oral$.tw. | 674828 |
| 10 | intraoral$.tw. | 13495 |
| 11 | buccal$.tw. | 27598 |
| 12 | sublabial$.tw. | 412 |
| 13 | sublingual$.tw. | 11003 |
| 14 | supralingual$.tw. | 20 |
| 15 | intraocular$.tw. | 66762 |
| 16 | intra ocular$.tw. | 1921 |
| 17 | intracameral$.tw. | 1925 |
| 18 | intra cameral$.tw. | 20 |
| 19 | intravitreal$.tw. | 18222 |
| 20 | intra vitreal$.tw. | 112 |

| | | |
|---|---|---|
| 21 | ophthalm$.tw. | 103205 |
| 22 | exp gels/ | 52189 |
| 23 | drug implants/ | 9197 |
| 24 | lozenge?.tw. | 1142 |
| 25 | troche?.tw. | 166 |
| 26 | film?.tw. | 174783 |
| 27 | ((eye? or ocular$) adj3 (gel? or implant$ or infus$ or inject$ or insert$ or instill$)).tw. | 8422 |
| 28 | or/6-27 | 1155591 |
| 29 | and/5,28 | 371 |
| 30 | exp animals/ not humans/ | 4732434 |
| 31 | 29 not 30 | 315 |
| 32 | limit 31 to english language | 287 |

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: September 10, 2020
- Limits: Humans (search hedge); English language
- Number of results: 415

| | | |
|---|---|---|
| 1 | ‘tropicamide'/mj | 736 |
| 2 | ‘tropa acid amid*':ti,ab,tn | 0 |
| 3 | ‘tropicacyl':ti,ab | 2 |
| 4 | ‘tropicamid*':ti,ab | 1174 |
| 5 | ‘tropikamid*':ti,ab | 1 |
| 6 | #1 OR #2 OR #3 OR #4 OR #5 | 2725 |
| 7 | ‘buccal drug administration'/exp | 5166 |
| 8 | ‘oral drug administration'/de | 406337 |
| 9 | ‘intraocular drug administration'/exp | 12048 |
| 10 | ‘oral*':ti,ab | 970297 |
| 11 | ‘intraoral*':ti,ab | 17758 |
| 12 | ‘buccal*':ti,ab | 35450 |
| 13 | ‘sublabial*':ti,ab | 549 |
| 14 | ‘sublingual*':ti,ab | 16566 |
| 15 | ‘supralingual*':ti,ab | 27 |
| 16 | ‘intraocular*':ti,ab | 88830 |
| 17 | ‘intra ocular*':ti,ab | 3387 |
| 18 | ‘intracameral*':ti,ab | 2361 |
| 19 | ‘intra cameral*':ti,ab | 26 |
| 20 | ‘intravitreal*':ti,ab | 24743 |
| 21 | ‘intra vitreal*':ti,ab | 256 |
| 22 | ‘ophthalm*':ti,ab | 162085 |

| | | |
|---|---|---|
| 23 | ‘gel'/exp | 77538 |
| 24 | ‘lozenge'/de | 1217 |
| 25 | ‘intravitreal implant'/de | 717 |
| 26 | ‘lozenge$':ti,ab | 1556 |
| 27 | ‘troche$':ti,ab | 248 |
| 28 | ‘film$':ti,ab | 177453 |
| 29 | ((eye$ OR ocular*) NEAR/3 (gel$ OR implant* OR infus* OR inject* OR insert* OR instill*)):ti,ab | 12025 |
| 30 | #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 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 | 1794564 |
| 31 | #6 AND #30 | 583 |
| 32 | [animals]/lim NOT [humans]/lim | 6086394 |
| 33 | #31 NOT #32 | 476 |
| 34 | #31 NOT #32 AND [english]/lim | 415 |

*Appendix 2.1. Survey instrument for professional medical associations*

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 drugs do you prescribe or administer to your patients? (please check all that apply)
    - o Acetylcysteine
    - o Bupivacaine hydrochloride
    - o Clonidine hydrochloride
    - o Tetracaine hydrochloride
    - o Triamcinolone acetonide
    - o Tropicamide
    - o None of the above
3. I prescribe or administer compounded [substance from question 2] in combination with other active pharmaceutical ingredients as a multi-ingredient product.
    - o Yes, please explain _____
    - o No
4. Do you prescribe or administer [substance from question 2] by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Local/perineural injection
    - o Intracameral injection
    - o Intraocular injection
    - o Ophthalmic solution, suspension, or gel
    - o Other (please describe) _____
    - o None of the above
5. I prescribe or administer [substance from question 2] for the following conditions or diseases:
    - o Anesthesia for ophthalmic procedures
    - o Dilation for mydriasis induction
    - o Dry eye caused by meibomian gland dysfunction
    - o Peribulbar or retrobulbar block
    - o Other, please explain _____
    - o None of the above
6. I prescribe or administer [substance from question 2] with my patients as the following;
    - o FDA-approved drug product
    - o Compounded drug product

- Over-the-counter drug product
- Other (please explain) _____

7. I used compounded [substance from question 2] 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) _____
   - I am not aware of any commercially available products containing [substance from question 2]
   - Other (please explain) _____
8. Do you stock non-patient-specific compounded [substance from question 2] at your practice?
   - Yes
   - No
   - I'm not sure
9. I obtain compounded [substance from question 2] 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) _____
10. What is your practice setting? (please check all that apply)
    - Physician office/private practice
    - Outpatient clinic
    - Hospital/health system
    - Academic medical center
    - Emergency room
    - Operating room
    - Other (please describe) _____
11. What degree do you hold? (please check all that apply)
    - Doctor of Medicine (MD)
    - Doctor of Osteopathic Medicine (DO)
    - Doctor of Medicine in Dentistry (DMD/DDS)
    - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - Naturopathic Doctor (ND)
    - Nurse Practitioner (NP)
    - Physician Assistant (PA)
    - Other (please describe) _____

*Appendix 2.2. Survey instrument for pharmacy roundtable prequestionnaire*

1. Please select all that apply regarding the facility with which you are affiliated.
    - Academic medical center
    - Acute care hospital
    - Children's hospital
    - Community hospital
    - Critical access hospital
    - Dialysis center
    - Federal government hospital
    - Health system
    - Inpatient rehabilitation center
    - Long-term acute care hospital
    - Outpatient surgery center
    - Rural hospital
    - Skilled nursing facility
    - Specialty hospital, please identify specialtiy(ies)
    - Trauma center
    - Urban hospital
2. Please select the number of beds in the facility with which you are affiliated.
    - < 50
    - 50-99
    - 100-199
    - 200-299
    - 300-399
    - 400-599
    - > 600
3. Do you use an outsourcing facility (503b facility) to obtain any products used in your facility? A list of FDA registered outsourcing facilities can be found at https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilites.
    - Yes
    - No
4. Why do you use an outsourcing facility to obtain product(s)? Please select all that apply
    - Backorders
    - Convenience
    - Cost
    - Need for concentrations not commercially available
    - Need for preservative-free products
    - Need for ready-to-use products
    - No FDA-approved products available
    - No onsite compounding facility
    - Onsite compounding facility not equipped to compound all necessary products
    - Other, please explain _____
5. Please select the type(s) of products obtained from an outsourcing facility.
    - Nonsterile products
    - Sterile products
6. Please select the category(ies) of products obtained from an outsourcing facility.
    - Cardioplegic solutions
    - Dermatologic preparations
    - Dialysate solutions

- Fluids
- Ophthalmic preparations
- Patient-controlled analgesia
- Ready-to-use anesthesia syringes
- Ready-to-use antibiotic syringes and/or bags
- Ready-to-use electrolyte solutions
- Ready-to-use vasopressor solutions
- Total parenteral nutrition solutions
- Other, please identify _____

7. From the list below, please select the drug(s) that you obtain as either a single ingredient or multi-ingredient product from an outsourcing facility.
    - Acetylcysteine
    - Adenosine
    - Aluminum potassium sulfate
    - Aspartic acid
    - Atenolol
    - Atropine
    - Baclofen
    - Betamethasone
    - Biotin
    - Bupivacaine
    - Calcium chloride
    - Caffeine sodium benzoate
    - Cholecalciferol
    - Chromium chloride
    - Clonidine
    - Dexamethasone sodium phosphate
    - Diclofenac
    - Gentamicin
    - Glycerin
    - Hydroxyzine
    - Ketamine
    - Levocarnitine
    - Lidocaine
    - Lorazepam
    - Magnesium sulfate
    - Manganese chloride
    - Methylprednisolone
    - Midazolam
    - Mupirocin
    - Norepinephrine
    - Ondansetron
    - Phytonadione
    - Potassium chloride
    - Potassium phosphate
    - Prilocaine
    - Proline
    - Propranolol
    - Ropivacaine
    - Sodium chloride
    - Sodium citrate

- Sodium phosphate
- Tetracaine
- Triamcinolone acetonide
- Tropicamide
- None of the above

*Appendix 3. Survey distribution to professional associations*

| Specialty | Association[a] | Agreed/Declined, Reason for Declining |
|---|---|---|
| Anesthesiology | Society of Cardiovascular Anesthesiologists | Declined – failed to respond |
| Cardiology | American Academy of Cardiovascular Perfusion | Declined |
| | American Board of Cardiovascular Perfusion | Declined – failed to respond |
| | American Society of Extracorporeal Technology | Declined – failed to respond |
| Dermatology | American Academy of Dermatology | Declined – failed to respond |
| Naturopathy | American Association of Naturopathic Physicians | Agreed |
| Nephrology | American Society of Diagnostic and Interventional Nephrology | Declined |
| Ophthalmology | American Academy of Ophthalmology | Declined – failed to respond |
| | American Society of Cataract and Refractive Surgery | Agreed |
| | American Society of Retina Specialists | Declined |
| Podiatry | American Podiatric Medical Association | Agreed |
| Psychiatry | The International Society for Electroconvulsive Therapy and Neurostimulation | Agreed |
| Rheumatology | American College of Rheumatology | Agreed |
| Surgery | American Association of Neurological Surgeons | Declined – failed to respond |
| | American Association for Thoracic Surgery | Declined – failed to respond |
| | American College of Surgeons | Declined – failed to respond |
| | American Society for Reconstructive Microsurgery | Declined – failed to respond |
| Urology | Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction | Declined |
| Wound Care | Association for the Advancement of Wound Care | Declined – failed to respond |

[a]Associations that declined in Year 1 and/or Year 2 were not contacted in Year 3.