Summary Report

Phenylephrine hydrochloride

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 2U01FD005946

Prepared by:

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February 2020

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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REVIEW OF NOMINATIONS

Phenylephrine hydrochloride (phenylephrine HCl; UNII code: 04JA59TNSJ) was nominated for inclusion on the 503B Bulks List by Rebecca Mitchell, Fagron, Specialty Sterile Pharmaceutical Society (SSPS), Athenex, Pine Pharmaceuticals, Outsourcing Facilities Association (OFA), Pentec Health, American Society for Cataract and Refractive Surgery (ASCRS), American Society of Retina Specialists (ASRS), and American Academy of Ophthalmology (AAO).

Phenylephrine was nominated for use in combination with additional active pharmaceutical ingredients (API), refer to Table 7 for the nominated combination formulations.

As an API, phenylephrine HCl is utilized to treat a vast array of medical conditions which may be unknown to the 503B facility. Based on the prescriber's request and what the prescriber is intending to treat the route of administration (ROA) will vary, including intravenous, nasal, topical, and rectal. The compounded dosage forms may include ophthalmic ointments, drops, gels, irrigations, and injections in concentrations ranging from 0.051-10% alone and in combination with additional API; 0.1mg/mL intravenous injection; 1.5% intra-ocular injection in combination with lidocaine; 0.125-1% nasal sprays alone and in combination with additional API; oral topical gels; orally disintegrating strips; capsules; 0.25-2% topical gels and ointments alone and in combination with additional API; and 0.25% rectal ointments, creams, suppositories and gels alone and in combination with additional API.

Additionally, phenylephrine HCl was nominated for use in glaucoma, hypotension during anesthesia, hypotension - shock, mydriasis induction, posterior synechiae - uveitis, mydriasis induction (maintenance), paroxysmal supraventricular tachycardia, priapism, regional anesthesia (adjunct), spinal anesthesia, nasal congestion, hemorrhoids, and eustachian tube congestion as a 0.01-100mg/mL preservative-free and preserved solution for intravenous, intramuscular, subcutaneous, intra-ocular, intracameral, topical, and ophthalmic administration.

Phenylephrine HCl was also nominated for use as a 2.5% ophthalmic solution in combination with tropicamide for mydriasis. Lastly, phenylephrine HCL was nominated for use as a 2.5-10% preservative-free topical ophthalmic solution to dilate the pupil and a 1.5-3% intracameral injection for pupil dilation during intraocular surgery, particularly in cases of intraocular floppy iris syndrome.

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

- Manufacturer backorder.
- When a different strength, dosage form, or ready-to-use packaging is required by a facility or practitioner.
- There are no FDA-approved combination products with tropicamide and phenylephrine. Studies have shown that a mixture of phenylephrine and tropicamide leads to more effective and wider pupil dilution than using either alone or alternating therapy.
- Combination eye drops allow for ease of administration, reduce the likelihood of allergic reactions, and improve adherence.
- It is relatively unsafe to expose the direct compounding area to hundreds of vials or ampules and hundreds of aseptic manipulations during the compounding of a typical batch size for an outsourcing facility; compounding from bulk is safer and more efficient.
- Commercially available finished products have an inherent variance in potency creating an uncertain final concentration for the new product.
- Use of state-of-the-art equipment, like the SKAN isolator technology, requires the use of bulk starting materials.

- Possible patient sensitivities to dyes, fillers, preservatives, and other excipients in manufactured products. For example, the topical and injectable formulations of commercially available phenylephrine contain sodium metabisulfite which is toxic to the corneal endothelium.
- The commercially available product must be used within four (4) hours if stored at room temperature and 24 hours if refrigerated after dilution. A compounded product can provide an increased timeframe in which the product can be used.
- As with any drug product, patients respond differently. The compounded product may be the only product to effectively treat the indication for which it is intended to treat.
- Phenylephrine is more stable than epinephrine and is not subject to the degradation in the typical time frame between compounding and use.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of phenylephrine HCl products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, 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 phenylephrine HCl; name variations of phenylephrine HCl were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing phenylephrine HCl. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

<u>Search strategy</u>

A medical librarian constructed comprehensive search strategies for PubMed and Embase. Two search strategies were designed for each database (see Appendix 1 for complete search strategies). The first search strategy used controlled vocabulary terms with subheadings for phenylephrine HCl, combined with controlled vocabulary terms and keywords for nominated ROA. The second search strategy used controlled vocabulary terms and keywords for each of three concepts: phenylephrine

HCl; ROA; and substances nominated for use in combination with phenylephrine HCl. Results were limited to original research articles or conference abstracts in English language. All searches were conducted on July 24, 2019. Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence for screening.

Study selection

Literature reviews and/or meta-analyses, cost-effectiveness, and epidemiological studies were excluded. Phenylephrine HCl is a component of an FDA-approved product, as a result, articles were excluded if phenylephrine HCl was utilized as the FDA-approved product or in the same concentration and formulation as the FDA-approved product. Articles were considered relevant based on the identification of a clinical use of phenylephrine HCl or the implementation of phenylephrine HCl in clinical practice. Articles were excluded if not in English, a clinical use was not identified, incorrect salt form, or if the study was not conducted in humans. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

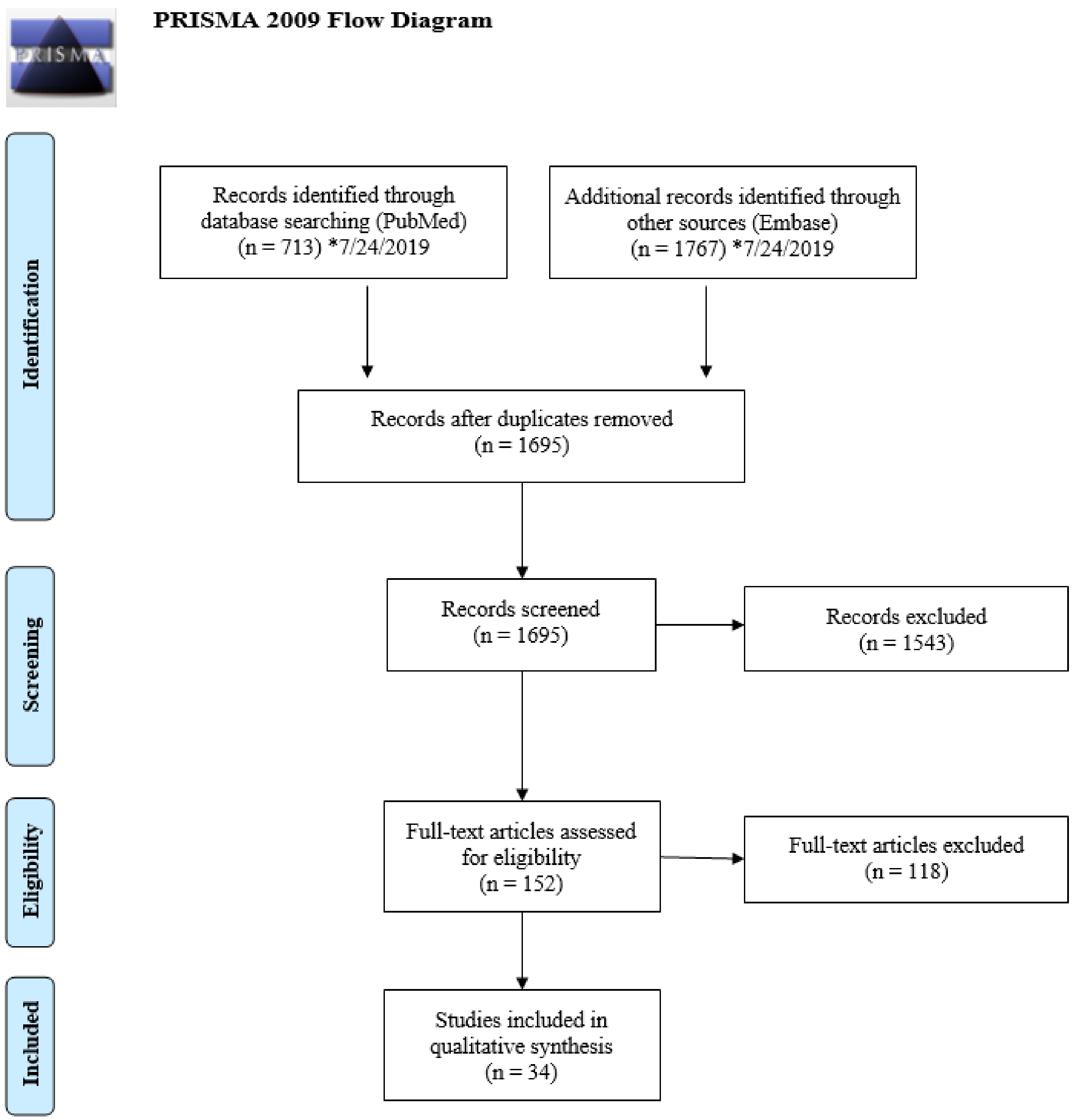
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for phenylephrine HCl use; dose; strength; dosage form; ROA; frequency and duration of therapy; any combination therapy utilized; if applicable, formulation of compounded products; study design; and any discussion surrounding the use of phenylephrine HCl compared to alternative therapies.

Results

Please refer to Figure 1.

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



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Outreach to medical specialists and specialty organizations

Using the indications from the nominations and the results of the literature review, nine (9) medical specialties that would potentially use phenylephrine HCl were identified: anesthesiology, cardiology, critical care, gastroenterology, ophthalmology, otolaryngology, pain management, primary care, and proctology. Semi-structured interviews were conducted with subject matter experts within these specialties. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. Six (6) experts were contacted for interviews, of which four (4) accepted. One (1) expert specializing in gastroenterology replied via email that phenylephrine is rarely as a topical treatment for hemorrhoids, no further follow-up was warranted. One (1) expert specializing in otolaryngology failed to respond to the interview request. Interviews were recorded and transcribed via ©Rev.com. QSR International's NVivo 12 software was utilized for qualitative data analysis. The University of Maryland, Baltimore IRB and the Food & Drug Administration RIHSC reviewed the study and found it to be exempt. Subject matter experts provided their oral informed consent to participate in interviews.

Survey

General professional medical associations and specialty associations for anesthesiology, cardiology, critical care, gastroenterology, ophthalmology, otolaryngology, pain management, primary care, and proctology, identified from the nominations, literature review, and interviews, were contacted to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within each specialty. Associations were included if their members are predominantly practitioners, national associations, and organizations focused on practice within the US. Organizations without practicing physicians and state or regional organizations were excluded. The association's website was searched in order to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used.

An online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to 16 associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

Participation was anonymous and voluntary. The estimated time for completion was 30 minutes with a target of 50 responses per survey. The Office of Management and Budget (OMB) approved this project.

Table 1. Participating associations

Specialty	Association
Ophthalmology	American Academy of Ophthalmology (AAO)
	American Society of Cataract and Refractive Surgery (ASCRS)
	American Society of Retina Specialist (ASRS)
Pain Medicine	American Academy of Pain Medicine (AAPM)
Primary Care	American Academy of Environmental Medicine (AAEM)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Anesthesiology	American Society of Anesthesiologists (ASA)	Declined, requires a PI who is a member
Critical Care	Society of Critical Care Medicine (SCCM)	Declined, "this project is so unique that SCCM may not be the audience; the link between improvement in ICU care is very remote and does not justify the study”
Gastroenterology	American Gastroenterological Association (AGA)	Failed to respond
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Failed to respond
	American Academy of Otolaryngic Allergy (AAOA)	Declined, stating otolaryngologists were not the target market for the survey
	American Rhinologic Society (ARS)	Declined, requires a request from a member; unable to identify a member to request survey distribution
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond
Proctology	American Society of Colon and Rectal Surgeons (ASCRS)	Declined, survey not approved for distribution

CURRENT AND HISTORIC USE

Summary of background information

- Phenylephrine HCl is available as an FDA-approved product.
- Phenylephrine HCl is available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for phenylephrine HCl.
- Phenylephrine HCl is available in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Namibia, New Zealand, and UK (see Table 4). In Latvia and Saudi Arabia, phenylephrine HCl is available as an OTC product.

Table 3. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	ROA	Status	Approval Date[b]
Phenylephrine HCl	0.1-10mg/mL	Solution	Intravenous	Prescription	6/27/2014
	2.5-10%	Solution/drops	Ophthalmic		3/21/2013

Abbreviations: "–", not mentioned; ROA, route of administration.
[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

Table 4. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	ROA	Approved For Use		
				Country	Status	Approval Date[b]
Phenylephrine HCl	10mg/mL	Injection	–	Abu Dhabi	Active	–
				Hong Kong	Prescription	12/14/1998
	50mcg/mL, 10mg/mL	Solution				10/25/2013
	50mcg/mL			Ireland	Prescription, non-renewable	11/27/2015

	10mg/mL			New Zealand	Prescription	4/4/1997
	10mg/mL, 10mg	Solution	Intramuscular, subcutaneous	Australia	Schedule 4	9/10/1991
				Canada	Ethical	12/31/1992
				UK	Prescription	11/17/1999
	0.1-10mg/mL, 10mg	Solution	Intravenous	Australia	Schedule 4	9/10/1991
	50mcg/mL, 10mg/mL			Belgium	Prescription	12/17/2015
	10-50mg/mL			Canada	Ethical	12/31/1992
	0.1-10mg/mL, 50mcg			UK	Prescription	11/17/1999
	2.5-100mg/mL	Drop	Nasal	Abu Dhabi	Active	–
	0.5-5mg/mL	Spray				
	5mg/mL			Australia	–	9/10/1991
	10mg	Tablet		New Zealand	Pharmacy-only medicine[c]	5/25/2006
	2.5-100mg/mL	Drop	Ophthalmic	Abu Dhabi	Active	–
	25mg/mL			Australia	Schedule 2	9/15/1993
	100mg/mL				Schedule 4	10/30/1991
	150mg/mL, 50mg			Belgium	Prescription	8/31/1971
	100mg/mL			Canada	Prescription	12/31/1985
	25mg/mL			Ireland	Prescription, renewable	4/19/1990
	1.2mg/mL			Namibia	–	12/23/1976

	30mg/mL			New Zealand	Pharmacy-only medicine[c]	9/6/1989
	100mg/mL				Prescription	
	25-100mg/mL			UK	Pharmacy-only medicine[c]	5/12/1986
	10-12.2mg	Capsule	Oral	Australia	Schedule 2	8/24/2007
Phenylephrine HCl / Tropicamide	5.38mg / 0.28mg	Ophthalmic insert	Ophthalmic	Belgium	Prescription	1/2/2008
	5.4mg / 0.28mg			UK		12/8/2009

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

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

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

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

Summary of literature review

- Total number of studies included: 34 studies (2 descriptive, 31 experimental, and 4 observational).
- Most of the studies were from Sweden and US (9 studies each).
- The most common indication for the use of phenylephrine HCl in the US was anesthesia. The most common indication from the non-US studies was mydriasis.
- Compounded products were identified from both US and non-US studies, all of which were used in nominated formulations.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[1,2]	2
Experimental[3-30]	31
Observational[31-34]	4

Table 6. Number of studies by country

Country	Number of Studies
Bosnia and Herzegovina[31]	1
France[32]	1
India[2,22,25]	3
Italy[23]	1
Mexico[34]	1
South Korea[21]	1
Spain[13]	1
Sweden[4-6,12,14-17,29,30]	9
Switzerland[7]	1
UK[1,8,9,28,33]	5
US[3,10,11,18-20,24,26,27]	9
	Total US: 9 Total Non-US Countries: 24

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Phenylephrine HCl 1% / Dibucaine HCl 0.5% / Lidocaine 15% / Prilocaine 5% - Topical ointment	0
	Phenylephrine HCl 0.25% / Lidocaine 15% / Prilocaine 5% - Topical ointment	0
	Phenylephrine HCl 2.5-10% / Tropicamide - Ophthalmic solution/drop[2,22,23,25,34]	5
	Phenylephrine HCl 2.5% / Tropicamide 0.5-1% - Ophthalmic solution[3,7,31]	3
Others found in literature	Phenylephrine HCl 1.5% / Cyclopentolate 0.85% - Ophthalmic solution[4,5,30]	2
	Phenylephrine HCl 2.5% / Cyclopentolate 0.5% - Ophthalmic solution[3]	1
	Phenylephrine HCl 2.5% / Cyclopentolate 0.75% - Ophthalmic[29]	1
	Phenylephrine HCl 1.5% / Cyclopentolate 0.1% / Lidocaine 1% - Intracameral solution[4,5,14,15,20]	4
	Phenylephrine HCl 200mcg / Lidocaine 4% - Nasal solution[11]	1
	Phenylephrine HCl 0.25% / Lidocaine 3% - Nasal solution[10]	1
	Phenylephrine HCl 0.5% / Lidocaine 4% - Intranasal solution[24]	1
	Phenylephrine HCl 0.5% / Lidocaine 5% - Intranasal aerosol[18,28,33]	3
	Phenylephrine HCl 1% / Lidocaine 4% - Intranasal[19]	1
	Phenylephrine HCl 1.5% / Lidocaine 1% - Intracameral solution[12,16,17]	3
	Phenylephrine HCl 2.5% / Lidocaine 1% / Tetracaine 1% - Topical[27]	1
	Phenylephrine HCl 5% / Lidocaine 1% / Tetracaine 1%[26]	1
	Phenylephrine HCl 10% / Lidocaine 1% / Tropicamide 0.5% - Intracameral solution[32]	1

	Phenylephrine HCl 0.99% / Prilocaine 3.56%[26]	1
	Phenylephrine HCl 5% / Tetracaine 1%[26]	1

Table 8. Dosage by indication – US

Indication	**Dose**	**Concentration**	**Dosage Form**	**ROA**	**Duration of Treatment**
Anesthesia[10,11,18,19,26,27]	0.5ml	0.25%	Solution	Nasal/intranasal	Once
	–	200mcg			
	3ml	0.5%	Aerosol		
	–	1%	–		–
	–	2.5%	–	Topical	Once
	–	0.99-5%	–	–	Once
Mydriasis[3,20]	1 drop	2.5%	Solution	Ophthalmic	Once
	0.3ml	1.5%		Intracameral	
Nasal dilation[24]	0.6ml	0.5%	Spray	Intranasal	Once

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

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Mydriasis[2,4-7,12,14-17,22,23,25,29-32,34]	0.05-0.2ml	0.015-10%	Solution	Intracameral	Once
	1-3 drops	1.5-5%	Solution	Ophthalmic	Once – 2 times
	1-3 drops	2.5-10%	–	Ophthalmic	Once – 4 times
	–	5%	Solution	Topical	6 weeks
Fecal incontinence[8,9,21]	1ml/day	10-30%	Gel	Topical	4 weeks
Anesthesia[28]	0.39ml	0.5%	Spray	Nasal	Once
Prevent intraoperative floppy iris syndrome[13]	0.6ml	1.5%	Solution	Intracameral	Once
Drug-induced sleep endoscopy[33]	2 puffs/nostril	0.5%	Spray	Nasal	Once
Intraoperative intraocular bleeding[1]	0.3ml	2.5%	Solution	Intracameral	Once

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

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Anesthesia[18]	1989	• "Prepared by a pharmacist"	Aerosol	0.5%
Mydriasis[3]	1980	• "Prepared here"	Solution	2.5%
Nasal dilation[24]	1986	• "Prepared in our pharmacy"	Spray	0.5%

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Mydriasis[4-6,12,14,16,17,31]	• "Prepared by pharmacy from sterile salts" • Prepared by the pharmacy from sterile salts, a mixture of 150 mcl phenylephrine 1.5% and lidocaine 1% • "Prepared in pharmacy"	Solution	1.5-2.5%
	• Sterile phenylephrine HCl dissolved in a balaced salt solution, double distilled and deionized water added, pH adjusted to 7 using sodium hydroxide • "Phenylephrine HCl 15mg, lidocaine HCl 10mg, sodium edetase 1mg, boric acid 3.85mg, aqua injectabile qs ad 1ml *[sic]*" • "Cyclopentolate HCl 1mg, phenylephrine HCl 15mg, lidocaine HCl 10mg, sodium edetase 1mg, boric acid 3.85mg, aqua injectabile qs ad 1ml *[sic]*"	Preservative free solution	0.015-3%
Fecal incontinence[21]	• 3g of phenylephrine HCl in 7g of white petrolatum	Gel	30%
Prevent intraoperative floppy iris syndrome[13]	• Phenylephrine HCl 750mg, balanced salt solution 50ml	Preservative free solution	1.5%

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

Four (4) experts were interviewed; one (1) interview was conducted with two (2) interviewees simultaneously.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Phenylephrine HCl	Interview Summary Response
OPH_08	MD	Ophthalmology	Private practice	Yes	• Has used it for dilating pupils in vitrectomy, for patients who have pupils that do not dilate well. • 0.5mL of intracameral drops or infusion solution, concentration of 1:1000.
ANE_01	MD	Anesthesiology	Trauma center	Not specified	• Commercially available phenylephrine is suitable.
ANE_02	NP	None	Trauma center	Not specified	• Commercially available phenylephrine is suitable.
OPH_05	MD	Ophthalmology	Academic medical institute	Yes	• Usually administer proparacaine first, check pressure to see if the eye is numb, then administer a drop of tropicamide, then a drop of phenylephrine to dilate the eye. • Has never used a combination compounded product because not sure about half-life and beyond use date of the product. • Can understand why some people prefer putting in less drops. • Reasoning for using a higher concentration may be to numb the eye more but has not had a patient where this was necessary.

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

Supply

- One (1) interviewee stated, “In the hospital, they’re not using the eyedrops. They’re getting phenylephrine, I guess maybe in an intravenous form.”

Combination use

- One (1) interviewee stated that some ophthalmologists like to use compounded phenylephrine and cyclopentolate together, particularly for children, so they can get one (1) single drop instead of two (2) separate drops.
- One (1) interviewee could not comment on the use of phenylephrine 1.5% / cyclopentolate 0.1% / lidocaine 1% because the interviewee was not a cataract surgeon.
- For one (1) interviewee, it was marketed as a combination compounded product (phenylephrine / proparacaine / tropicamide), but never used because the interviewee was not sure about the half-life or the beyond-use-date of the product. Had not seen it used in combination with proparacaine and cyclopentolate, and not sure if it is chemically okay for them to be combined together.

Use as an ointment

- One (1) interviewee stated, “The ointment I have no knowledge of. I’ve never heard of that being used in an ointment, so I’m not sure why that would be used.’

Office use

- One (1) interviewee stated “In the office setting, we would have a bottle and we would use it multiple times. In the operating room setting, typically the rules are more stringent, and the practice is different. So typically, it’s a different bottle for every patient.”

Summary of survey results

Table 13. Characteristics of survey respondents [71 people responded to the survey[a]]

Board Certification	MD	NP	RPh	No Response
Anesthesiology	1	0	0	0
Cardiovascular Disease	0	1	0	0
Internal Medicine	1	0	0	0
Neurology	1	0	0	0
Ophthalmology	36	0	0	0
Pain Medicine	3	0	0	0
No Board Certification	1	0	1	0
No Response	0	0	0	29

Abbreviations: MD, Doctor of Medicine; NP, Nurse Practitioner; RPh, Registered Pharmacist.
[a]Some respondents reported more than one (1) terminal clinical degree or board certification.

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

Types of Products	Respondents, n (N=61[a])
Compounded	18[b]
FDA-approved	35
Over-the-counter	0
Dietary	0
Unsure	3
No Response	18

[a]Out of 71 respondents, 61 reported using, prescribing, or recommending multiple types of phenylephrine HCl product.
[b]Eleven (11) respondent used in combination. See Figure 2 below.

Figure 2. Compounded combinations reported in the survey

Active ingredients in combination products:

- "Cyclogel and atropine"
- Phenylephrine HCl 0.5-10% / Cyclopentolate / Tropicamide
- Phenylephrine HCl 1.5% / Lidocaine 1%
- Phenylephrine HCl 0.12% / Pyrilamine maleate / Zinc sulfate
- Phenylephrine HCl 2.5-10% / Tropicamide 0.5-1%

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

Indication	Strength	Dosing Frequency[b]	Dosage Form	ROA[b]	Duration of Treatment	Patient Population
Cataract surgery	2.5%	"Q5min x3"	Drop	"Operative eye"	Presurgical	Cataract surgery patients
		–	–	Topical, intracranial, intracameral	–	–
	–	"Intra op"	Drops	Intracameral	For surgery	Cataracts
Choroidal effusion, routine exam	–	–	–	–	–	–
Clinical exam	1%	Once	–	Topical	Once	All patient who needs dilated exam
Diagnostic use	2.5%	–	–	Topical	–	–
Dilation of pupils	2.5%	TID	Drops	Topical	One day	Cataract patients
		–		Both eyes	Once	Patients requiring dilation in office
						Office dilation in kids
				–		Almost every patient having a complete eye exam in the office
	–	As needed		Topical, ocular	For examination	Adults and children
			Sterile solution	Intraocular	As needed for surgery	Adult
Floppy iris syndrome	2.5%	Once	Solution	Intracameral	During surgery	Cataract surgery
	–	Single use	–	Intraocular	Single use in surgery	–
Fundus exam routine care	2.5%	–	–	Topical	–	–
Priapism reversal from ICI therapy	1mg/ml	As needed	Injectable	Intracavernosal	Ongoing	Adult men with ED

Pupillary miosis	–	Single use	–	Intraocular	Single use in surgery	–

Abbreviations: "– ", not mentioned; ICI, intracavernosal injection; ROA, route of administration; TID, three times per day.
[a]Fourteen (14) respondents.
[b]Quotations are direct words from respondents.

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

Indication	Standard Therapy			
	Compounded, n (N=18)	**Non-compounded, n (N=22)**	**Unsure, n (N=3)**	**No Response, n (N=18)**
Dilation in clinic[b]	5	17	2	0
Cataract surgery	2	1	0	0
Diagnostic use	1	2	0	0
Erectile dysfunction	1	0	0	0
Examination in office	0	1	0	0
Floppy iris syndrome	3	0	0	0
Intraoperative use for miosis	1	0	0	0
Pre-operative	1	0	0	0
Reversal of priapism caused by ICI therapy	1	0	0	0
Surgery	0	1	0	0
No Response	6	1	1	18

[a]Some respondents reported more than one indication.
[b]Includes: Dilation to evaluate patients for surgery; stabilize pupil during surgery; routine eye exams, laser surgeries, or cataract surgery; prior to cataract surgery; diagnostic test in scleritis.

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

Theme	Reasons
Availability	• "Available" • "No FDA-approved drug product available" • "None available" • "There is not an approved product that actually works" • "No approved med for intra operative use"
Cost	• "Cheaper price" • "Cost"
Convenience	• "Easier for patients to get combined drops" • "When doing cataract surgery at our ASC, the drops are compounded to allow for only one eye drop to be placed in the eye rather than 3 different drops" • "Combination compounded drop easier to administer than using two different drops and waiting between drops" • "Less drops for patient and nurses; effective for floppy iris syndrome"
Concentration	• "The FDA approved product is 10 times more concentrated than the compounded drug" • "Concentration 10 times different"

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

	Respondents, n (N=18)
No–use has remained consistent	3
Yes–I use it LESS often now	0
Yes–I use it MORE often now • "More need in surgery" • "Increases speed at which nurses can get patients ready for cataract surgery" • "It works" • "I like it during cataract surgery" • "Other medications with similar effect not available" • "Easier access to compounded drug non and compounded combination dilating drops easier to administer" • "Lipo-phen replaced epi-sugarcaine *[sic]*" • "Cheaper cost for compounded eye drops for dilated eye exams" • "Increasing amount of ED patients"	14
No Response	1

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

	Respondents, n (N=18)
No	8
Yes	9
No Response	1

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

	Respondents, n (N=9)
In what practice location(s) do you stock non-patient-specific compounded phenylephrine HCl?	
No response	1
Physician office	5
Outpatient clinic	4
Emergency room	3
Operating room	4
Inpatient ward	0
How do you obtain your stock of non-patient-specific compounded phenylephrine HCl?	
No response	1
Purchase from a compounding pharmacy	3
Purchase from an outsourcing facility	4
Have the product compounded by an in-house pharmacy	1
Why do you keep a stock of non-patient-specific compounded phenylephrine HCl?	
No response	1
Convenience	4
Emergencies	3
Other (Routine use in office and surgery)	3

CONCLUSION

Phenylephrine HCl (UNII code: 04JA59TNSJ) was nominated for inclusion on the 503B Bulks List for various indications, dosage forms, ROA, and strengths. Phenylephrine HCl is approved in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Namibia, New Zealand, UK, and US.

From the literature review conducted, the most common indication for the use of phenylephrine HCl in the US was anesthesia. The most common indication from the non-US studies was mydriasis. Compounded products were identified in both US and non-US studies, all of which were used in nominated formulations.

Two (2) out of four (4) interviewees had used phenylephrine HCl in their practice, for the purpose of dilating pupils in vitrectomy. One (1) interviewee stated that some ophthalmologists like to use a compounded phenylephrine and cyclopentolate product, particularly for children, so only a single drop is needed instead of two separate drops. For one (1) interviewee, it was marketed as a combination compounded product (phenylephrine / proparacaine / tropicamide), but never used it because the interviewee was not sure about the half-life or the beyond-use-date of the product. The interviewee had not seen it used in combination with proparacaine and cyclopentolate, and not sure if it is chemically okay for them to be combined.

From the survey responses, 61 out of 71 respondents used phenylephrine HCl. The most common indications for use were pupil dilation and cataract surgery. Availability, cost, convenience, and concentration were some of the reasons for using the compounded phenylephrine HCl product over an FDA-approved product. Nine (9) out of 18 respondents who used compounded product reported stocking compounded phenylephrine HCl in the physician's office, outpatient clinic, emergency room, and operating room. Reasons for stocking non-patient specific compounded phenylephrine were convenience, emergencies, and routine use.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy 1

- Platform: PubMed
- Years searched: 1946 to present
- Limits: Humans (search hedge); English language
- Date searched: July 24, 2019
- Number of results: 462

1	Search ("phenylephrine/therapeutic use"[MeSH:noexp] OR "phenylephrine/administration and dosage"[MeSH:noexp])	1877
2	Search ("administration, intravenous"[MeSH] OR "injections, subcutaneous"[MeSH:noexp] OR "injections, intramuscular"[MeSH] OR "injections, intraocular"[MeSH] OR "therapeutic irrigation"[MeSH] OR "administration, topical"[MeSH] OR "administration, oral"[MeSH] "skin cream"[MeSH] OR "suppositories"[MeSH] OR injection[tiab] OR injections[tiab] OR injectable[tiab] OR intravenous*[tiab] OR subcutaneous*[tiab] OR intramuscular*[tiab] OR intraocular*[tiab] OR intracameral*[tiab] OR topical*[tiab] OR intranasal*[tiab] OR nasal[tiab] OR rectal*[tiab] OR irrigation[tiab] OR oral*[tiab] OR ointment[tiab] OR gel[tiab] OR spray[tiab] OR cream[tiab] OR suppository[tiab] OR suppositories[tiab]	2145347
3	Search ("animals"[MeSH] NOT "humans"[MeSH])	4602105
4	Search (#1 AND #2)	675
5	Search (#4 NOT #3)	504
6	Search (#5 AND English[lang])	462

MEDLINE search strategy 2

- Platform: PubMed
- Years searched: 1946 to present
- Limits: Humans (search hedge); English language
- Date searched: July 24, 2019
- Number of results: 251

1	Search ("phenylephrine/therapeutic use"[MeSH:noexp] OR "phenylephrine/administration and dosage"[MeSH:noexp] OR phenylephrin*[tiab] OR phenylefrin*[tiab] OR fenilefrina[tiab])	18990
2	Search ("administration, intravenous"[MeSH] OR "injections, subcutaneous"[MeSH:noexp] OR "injections, intramuscular"[MeSH] OR "injections, intraocular"[MeSH] OR "therapeutic irrigation"[MeSH] OR "administration, topical"[MeSH] OR "administration, oral"[MeSH] "skin cream"[MeSH] OR "suppositories"[MeSH] OR injection[tiab] OR injections[tiab] OR injectable[tiab] OR intravenous*[tiab] OR subcutaneous*[tiab] OR intramuscular*[tiab] OR intraocular*[tiab] OR intracameral*[tiab] OR topical*[tiab] OR intranasal*[tiab] OR nasal[tiab] OR rectal*[tiab] OR irrigation[tiab] OR oral*[tiab] OR ointment[tiab] OR gel[tiab] OR spray[tiab] OR cream[tiab] OR suppository[tiab] OR suppositories[tiab]	2145347

3	Search ("drug compounding"[MeSH] OR "dibucaine"[MeSH] OR "tropicamide"[MeSH] OR "cyclopentolate"[MeSH] OR "zinc sulfate"[MeSH] OR "pyrilamine"[MeSH] OR "benzocaine"[MeSH] OR "lidocaine"[MeSH] OR "tetracaine"[MeSH] OR "hydrocortisone"[MeSH:noexp] OR "prilocaine"[MeSH] OR dibucaine[tiab] OR cinchocain*[tiab] OR cincocainio[tiab] OR tropicamid*[tiab] OR cyclopentol*[tiab] OR ciclopentol*[tiab] OR "zinc sulfate"[tiab] OR "zinc sulphate"[tiab] OR pyrilamine[tiab] OR mepiramina[tiab] OR mepyramine[tiab] OR pyranisamine[tiab] OR benzocain*[tiab] OR lidocain*[tiab] OR lignocaine[tiab] OR tetracain*[tiab] OR amethocaine[tiab] OR dicaine[tiab] OR hydrocortison*[tiab] OR prilocain*[tiab] OR propitocaine[tiab])	141708
4	Search ("animals"[MeSH] NOT "humans"[MeSH])	4602105
5	Search (#1 AND #2 AND #3)	340
6	Search (#5 NOT #4)	272
7	Search (#6 AND English[lang])	251

Embase search strategy 1

- Platform: Elsevier
- Years searched: 1947 to present
- Limits: Humans (search hedge); Publication types: article, article in press, conference abstract, conference paper, conference review, data paper, review, short survey; English language
- Date searched: July 24, 2019
- Number of results: 1103

1	phenylephrine'/dd_ad,dd_do,dd_dt	4705
2	intravenous drug administration'/exp	389406
3	subcutaneous drug administration'/exp	100690
4	intramuscular drug administration'/exp	71259
5	intraocular drug administration'/exp	10732
6	topical drug administration'/exp	107782
7	oral drug administration'/exp	402419
8	rectal drug administration'/de	8541
9	irrigation solution'/de	302
10	drug dosage form'/exp	400487
11	injection$':ti,ab	809374
12	injectable$':ti,ab	24978
13	intravenous$':ti,ab	388883
14	subcutaneous$':ti,ab	184927
15	intramuscular$':ti,ab	55515
16	intraocular$':ti,ab	80015
17	intracameral$':ti,ab	1986
18	intranasal$':ti,ab	27386
19	topical$':ti,ab	129402
20	intranasal$':ti,ab	27386
21	rectal$':ti,ab	130609
22	oral$':ti,ab	802286

23	irrigation':ti,ab	32736
24	ointment':ti,ab	17370
25	spray':ti,ab	32108
26	gel':ti,ab	319574
27	cream':ti,ab	23688
28	eye drops':ti,ab	7759
29	suppositor*':ti,ab	6948
30	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	3542243
31	[animals]/lim NOT [humans]/lim	5873285
32	#1 AND #30	1662
33	#32 NOT #31	1310
34	#32 NOT #31 AND [english]/lim	1179
35	#32 NOT #31 AND [english]/lim AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [review]/lim OR [short survey]/lim)	1103

Embase search strategy 2

- Platform: Elsevier
- Years searched: 1947 to present
- Limits: Humans (search hedge); Publication types: article, article in press, conference abstract, conference paper, conference review, data paper, review, short survey; English language
- Date searched: July 24, 2019
- Number of results: 664

1	phenylephrine'/dd_ad,dd_do,dd_dt OR 'phenylephrin*':ti,ab,tn OR 'fenilefrina':ti,ab,tn	26531
2	intravenous drug administration'/exp	389406
3	subcutaneous drug administration'/exp	100690
4	intramuscular drug administration'/exp	71259
5	intraocular drug administration'/exp	10732
6	topical drug administration'/exp	107782

7	oral drug administration'/exp	402419
8	rectal drug administration'/de	8541
9	irrigation solution'/de	302
10	drug dosage form'/exp	400487
11	injection$':ti,ab	809374
12	injectable$':ti,ab	24978
13	intravenous$':ti,ab	388883
14	subcutaneous$':ti,ab	184927
15	intramuscular$':ti,ab	55515
16	intraocular$':ti,ab	80015
17	intracameral$':ti,ab	1986
18	intranasal$':ti,ab	27386
19	topical$':ti,ab	129402
20	intranasal$':ti,ab	27386
21	rectal$':ti,ab	130609
22	oral$':ti,ab	802286
23	irrigation':ti,ab	32736
24	ointment':ti,ab	17370
25	spray':ti,ab	32108
26	gel':ti,ab	319574
27	cream':ti,ab	23688
28	eye drops':ti,ab	7759
29	suppositor*':ti,ab	6948
30	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	3542243
31	cinchocaine'/exp	2861
32	tropicamide'/exp	2358

33	cyclopentolate'/exp	2003
34	zinc sulfate'/exp	6134
35	mepyramine'/exp	5750
36	benzocaine'/exp	3680
37	lidocaine'/exp	73161
38	tetracaine'/exp	7413
39	hydrocortisone'/exp	136267
40	prilocaine'/exp	4556
41	drug formulation'/de	115711
42	dibucaine':ti,ab,tn	1103
43	cinchocain*':ti,ab,tn	243
44	cincocainio':ti,ab,tn	0
45	tropicamid$':ti,ab,tn	1065
46	cyclopentolat*':ti,ab,tn	616
47	ciclopentolat*':ti,ab,tn	2
48	zinc sulphate':ti,ab,tn	1397
49	zinc sulfate':ti,ab,tn	2061
50	pyrilamine':ti,ab,tn	1427
51	mepyramine':ti,ab,tn	2179
52	mepiramina':ti,ab,tn	0
53	pyranisamine':ti,ab,tn	20
54	benzocain*':ti,ab,tn	1382
55	lidocain*':ti,ab,tn	28978
56	lignocaine':ti,ab,tn	3909
57	tetracain*':ti,ab,tn	2947
58	amethocain*':ti,ab,tn	319

59	dicaine':ti,ab,tn	99
60	hydrocortison*':ti,ab,tn	26666
61	prilocain*':ti,ab,tn	2191
62	propitocaine':ti,ab,tn	51
63	#31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62	356287
64	#1 AND #30 AND #63	882
65	[animals]/lim NOT [humans]/lim	5873285
66	#64 NOT #65	776
67	#64 NOT #65 AND [english]/lim	709
68	#64 NOT #65 AND [english]/lim AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [review]/lim OR [short survey]/lim)	664

Appendix 2. Survey instrument

Start of Block: Welcome Page

The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice. This survey is for **phenylephrine HCl**. As a medical expert, we appreciate your input regarding the use of this substance in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

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

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

End of Block: Welcome Page

Start of Block: Phenylephrine HCl

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **phenylephrine HCl**? Please check all that apply.

- ▢ Compounded drug product
- ▢ FDA-approved drug product
- ▢ Over the counter drug product
- ▢ Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- ▢ Unsure

Skip To: Q13 If What type(s) of product(s) do you use, prescribe, or recommend for phenylephrine HCl? Please check all th... != Compounded drug product

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

Display This Question:

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

Q2. Please list any conditions or diseases for which you use compounded **phenylephrine HCl** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q3. Do you use compounded **phenylephrine HCl** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- ▢ Single
- ▢ Combination

Skip To: Q5 If Do you use compounded phenylephrine HCl as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

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

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

- ▢ Phenylephrine HCl 0.01% / Benzocaine 20% / Lidocaine 6% / Tetracaine 4%
- ▢ Phenylephrine HCl 0.12% / Pyrilamine maleate / Zinc sulfate
- ▢ Phenylephrine HCl 0.25% / Hydrocortisone 1% / Lidocaine 2%
- ▢ Phenylephrine HCl 0.25% / Lidocaine 15% / Prilocaine 5%
- ▢ Phenylephrine HCl 1% / Dibucaine HCl 0.5% / Lidocaine 15% / Prilocaine 5%
- ▢ Phenylephrine HCl 1.5% / Lidocaine 1%
- ▢ Phenylephrine HCl 2% / Lidocaine 20% / Tetracaine 4%
- ▢ Phenylephrine HCl 0.5-10% / Cyclopentolate / Tropicamide
- ▢ Phenylephrine HCl 2.5-10% / Tropicamide 0.5-1%
- ▢ Other (please describe) ____

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

____

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

____

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

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

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

____

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

- o Yes
- o No

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

Display This Question:

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

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

- ▢ Physician office
- ▢ Outpatient clinic
- ▢ Emergency room
- ▢ Operating room
- ▢ Inpatient ward
- ▢ Other (please describe) ____

Q11. How do you obtain your stock of non-patient-specific compounded **phenylephrine HCl**? Please check all that apply.

- ▢ Purchase from a compounding pharmacy
- ▢ Purchase from an outsourcing facility
- ▢ Compound the product yourself
- ▢ Other (please describe) ____

Q12. Why do you keep a stock of non-patient-specific compounded **phenylephrine HCl**? Please check all that apply.

- ▢ Convenience
- ▢ Emergencies
- ▢ Other (please describe) ____

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

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

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

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

____

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

____

End of Block: Phenylephrine HCl

Start of Block: Background Information

Q15. What is your terminal clinical degree? Please check all that apply.

- ▢ Doctor of Medicine (MD)
- ▢ Doctor of Osteopathic Medicine (DO)
- ▢ Doctor of Medicine in Dentistry (DMD/DDS)
- ▢ Naturopathic Doctor (ND)
- ▢ Nurse Practitioner (NP)
- ▢ Physician Assistant (PA)
- ▢ Other (please describe) ____

Q16. Which of the following Board certification(s) do you hold? Please check all that apply.

- ▢ No Board certification
- ▢ Allergy and Immunology
- ▢ Anesthesiology
- ▢ Cardiovascular Disease
- ▢ Critical Care Medicine
- ▢ Dermatology
- ▢ Emergency Medicine
- ▢ Endocrinology, Diabetes and Metabolism
- ▢ Family Medicine
- ▢ Gastroenterology
- ▢ Hematology
- ▢ Infectious Disease
- ▢ Internal Medicine
- ▢ Medical Toxicology
- ▢ Naturopathic Doctor
- ▢ Naturopathic Physician
- ▢ Nephrology
- ▢ Neurology
- ▢ Obstetrics and Gynecology
- ▢ Oncology
- ▢ Ophthalmology
- ▢ Otolaryngology
- ▢ Pain Medicine
- ▢ Pediatrics
- ▢ Psychiatry

- ▢ Rheumatology
- ▢ Sleep Medicine
- ▢ Surgery (please describe) ____
- ▢ Urology
- ▢ Other (please describe) ____