Summary Report

Sildenafil citrate

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
ED	Erectile dysfunction
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
ODF	Oro-dispersible film
OTC	Over-the-counter
PDE5I	Phosphodiesterase type 5 inhibitor
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 sildenafil citrate (UNII code: 3M7OB98Y7H), 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 sildenafil citrate 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 sildenafil citrate 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 sildenafil citrate and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

Sildenafil citrate was nominated for inclusion on the 503B Bulks List by David Smith. Sildenafil citrate was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Sildenafil citrate was nominated for erectile dysfunction (ED) via an oral/sublingual troche combined with oxytocin. The sildenafil citrate strength in the compounded drug will range from 36-75 mg based on the prescriber's request; oxytocin strength will be based on the prescriber's request.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of sildenafil citrate.[6]

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

- There is an FDA-approved drug product as a tablet. The compounded drug product will be a different dosage form, sublingual troches, for those that many not be able to swallow. Also, different strengths, such as a higher strength than what is available, may be needed. The compounded drug product will also be combined with oxytocin in troche form, for which there are no approved drug products.
- Compounded drug products are requested by prescribers to treat individual patient needs. Here, a requesting physician has determined there is a clinical difference between the requested compounded drug and commercially available drug products.
- Compounding from the bulk drug substance means using only the ingredients necessary to achieve the desired clinical outcome as the API is used in its purest form without fillers, excipients, binders, dyes, preservatives, or other materials.
- Using a bulk drug substance instead of a finished product improves accuracy. A finished dosage form may have variance, often a 5-15% deviation from the labeled strength/potency permitted by USP monographs. The use of a finished product could introduce unacceptable inaccuracies into compounded medications.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of sildenafil citrate 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 sildenafil citrate; name variations of sildenafil citrate 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 sildenafil citrate. 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 three concepts: oxytocin; oral or sublingual administration; and therapeutic use for erectile or orgasmic dysfunction, or substances nominated for use in combination with, sildenafil citrate or tadalafil (refer to Appendix 1 for full search strategies). One search was constructed for three nominated substances, oxytocin, sildenafil citrate and tadalafil, because sildenafil citrate and tadalafil were only nominated for oral or sublingual use in combination with oxytocin. Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on April 10, 2020. The reference lists of relevant systematic reviews and meta-analyses were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on April 10, 2020 for clinical practice guidelines that recommended the use of sildenafil citrate and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which sildenafil citrate was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, 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 sildenafil citrate was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which sildenafil citrate 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 sildenafil citrate; setting; total number of patients; number of patients who received sildenafil citrate; patient population; indication for use of sildenafil citrate; dosage form and strength; dose; ROA; frequency and duration of therapy; use of sildenafil citrate in a combination product; use and formulation of sildenafil citrate in a compounded product; use of sildenafil citrate 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 sildenafil citrate was used in a clinical setting. The systematic literature review and indication from the nomination were reviewed to identify the following medical specialties that would potentially use sildenafil citrate: naturopathy and urology. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of sildenafil citrate in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to

identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

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

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

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

CURRENT AND HISTORIC USE

Results of background information

- Sildenafil citrate is not available as an FDA-approved product in the nominated dosage form and ROA.
- Sildenafil citrate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for sildenafil citrate.
- Sildenafil citrate is not available in the nominated dosage form and ROA in any of the foreign medical registries searched.

Table 1. Currently approved products – US

No approved products in the US

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

No approved products in the selected non-US countries and regions

Results of literature review

Study selection

Database searches yielded 46 references; 3 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 39 titles and abstracts were screened. After screening, the full text of 14 articles were reviewed. Finally, 0 studies were included. Fourteen studies were excluded for the following reasons: wrong study design (13 studies); unable to obtain (1).

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

Characteristics of included studies

No studies were included from the literature review.

Use of sildenafil citrate

No studies were included from the literature review.

Pharmacology and historical use

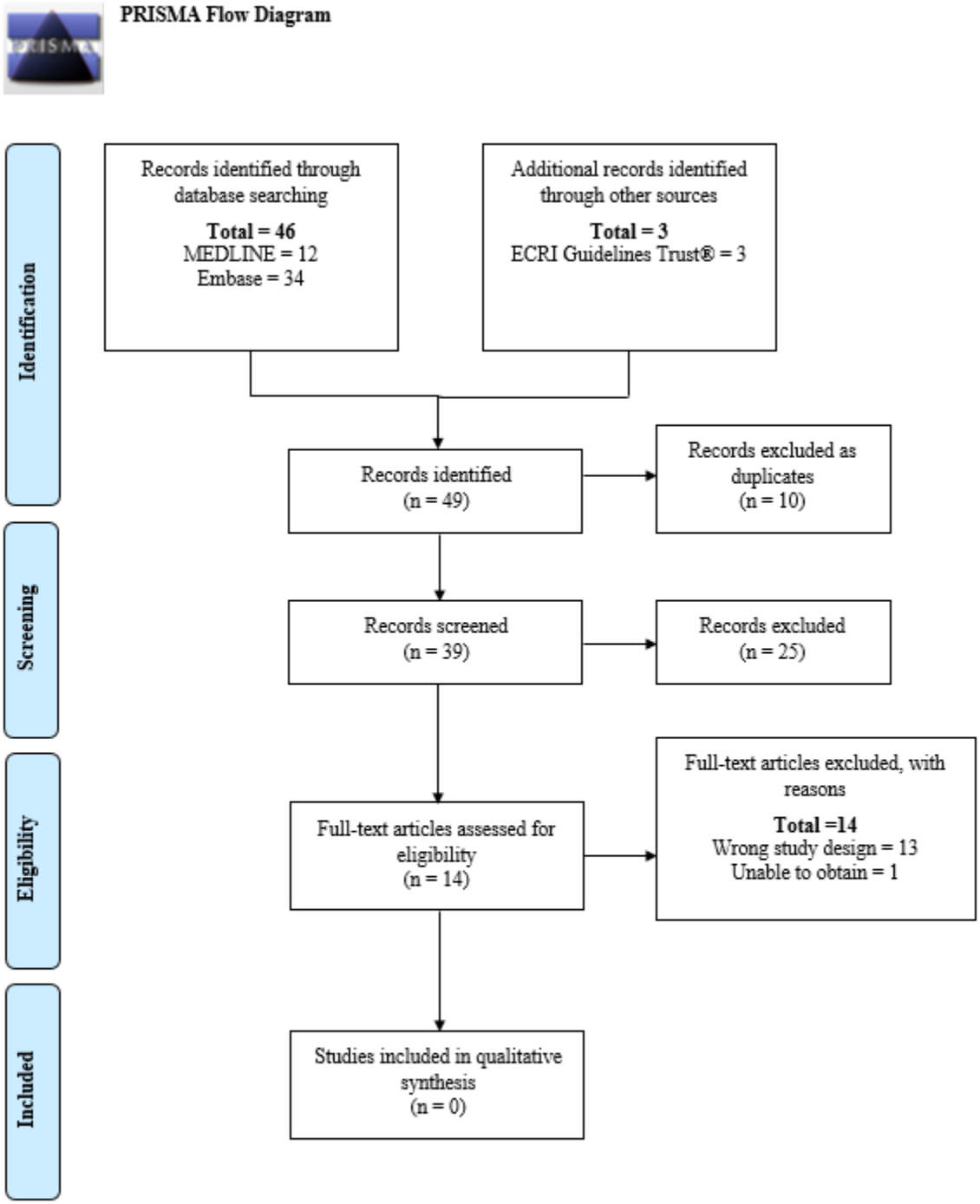
There were 7 studies identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of sildenafil citrate.

In 1998, sildenafil was introduced into the US market for management of ED.[7,8] The American Urological Association's 2018 guideline for ED included recommendations for prescription of an FDA-approved oral phosphodiesterase type 5 inhibitor (PDE5I).[9] Men prescribed an oral PDE5I for treatment of ED should be provided with instructions to maximize benefit and efficacy (strong recommendation; evidence level grade C) and the dose should be titrated to provide optimal efficacy (strong recommendation; evidence level B).[9] Sildenafil is one of the FDA-approved PDE5I for management of ED in the US.[9] Other options include tadalafil, vardenafil, and avanafil.[9] Pooled data across multiple trials and published systematic reviews suggest that all 4 PDE5I medications have a similar efficacy in the general ED population.[9] The most frequently reported adverse events for using PDE5I medications are "dyspepsia, headache, flushing, back pain, nasal congestion, myalgia, visual disturbance, and dizziness."[9] Most of the adverse event rates were similar across all 4 PDE5I medications with the "exception of dyspepsia (lowest rates reported with avanafil), flushing (lowest rates reported with tadalafil), and myalgia (lowest rates reported in vardenafil and avanafil)."[9] According to a 2016 review of treatment of neurogenic ED, oral PDE5I medications, including sildenafil, vardenafil, and tadalafil, have been generally safe and effective in select neurogenic ED populations, with the majority of the treatment effectiveness data from spinal cord injury patients.[8] Data for PDE5I medication use outside spinal cord injury population is lacking.[8]

Oxytocin, a neuropeptide, is known for its role in parturition and lactation[10,11] There has been interest in its potential role for arousal and orgasm since oxytocin plasma levels increase during sexual arousal and orgasm.[10] Per a 2015 review by Corona et al and a 2018 review by Kingsberg et al looking at sexual dysfunction, most studies looking at this potential role in humans have used intranasal oxytocin.[11,12] Both reviews concluded that further studies are still needed to examine the effects of oxytocin on sexual function in men and women.[10-12]

There were no studies found mentioning use of the nominated formulation of oxytocin as an oral/sublingual troche in combination with sildenafil citrate. The nominator included one study in the nomination that looked at sildenafil as an oro-dispersible film (ODF) for treatment of ED in 139 patients.[6] All patients were given sildenafil 100 mg tablet for 4 weeks and after a 2 week washout period, they took sildenafil 75 mg ODF for 4 weeks.[6] The mean score for overall satisfaction was in favor of the ODF formulation while the differences in mean International Index of Erectile Function scores for erectile function, orgasmic function, sexual desire, and intercourse satisfaction were significantly in favor of the sildenafil tablet formulation.[6] The authors concluded that the ODF formulation provides a new option for more precise tailored therapy and is safe and efficient with no additional side effects compared with the conventional tablet formulation.[6]

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

No studies included

Table 4. Number of studies by country

No studies included

Table 5. Summary of included studies

No studies included

Table 6. Dosage by indication – US

No studies included

Table 7. Dosage by indication – non-US countries

No studies included

Table 8. Number of studies by combination

	Combination Formula	**Number of Studies**
Nominated	Sildenafil citrate 36-75 mg/ Oxytocin – oral/sublingual troche	0

Table 9. Compounded products – US

No studies included

Table 10. Compounded products – non-US countries

No studies included

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Six SMEs discussed sildenafil citrate. Amongst these 6 SMEs, there were 4 medical doctors, 1 clinical psychologist, and 1 sexuality educator. The SMEs specialized and/or were board-certified in psychology, sexual/reproductive health, and urology, working in academic medical centers and private practice/clinics. The SMEs had been in practice for 8 to 45 years.

For the treatment of ED, the patient is usually first given a PDE5I such as Cialis® (tadalafil), Levitra® (vardenafil), Stendra® (avanafil), or Viagra® (sildenafil citrate). If that fails, then most patients will move to Trimix injection (alprostadil/papaverine/phentolamine). If the injections do not work, then a penile implant would be the next option.

Oxytocin can improve libido and overall sexual arousal. One SME called oxytocin a "cuddle drug" because it is a drug that can cause more intense orgasms and potentially reduce time to orgasm, especially in patients with delayed ejaculation. Another SME stated they do not use oxytocin frequently because there is currently not enough data, but they would consider oxytocin for orgasmic disorder.

For the nominated combinations of oxytocin with sildenafil citrate as an oral or sublingual troche, a couple of SMEs expressed they could see the value of having it. One SME elaborated that if this works, then it could be an alternative for the patients in which sildenafil is not working and who do not want to use injections. Another SME used oxytocin frequently as a 250 units lozenge that patients (man or woman) take 1 hour before sex and stated that oxytocin either works well or not at all. For men, this SME prescribes oxytocin with sildenafil and tadalafil, but not as a combination product. On the other hand, one SME pointed out that bioavailability is a factor to consider since oxytocin is a peptide. This means oxytocin cannot be easily put into pill as it will be destroyed by the stomach and intestines.

While topical sildenafil was not a nominated route of administration, a couple of SMEs mentioned that a topical sildenafil product in a phase IIB trial is being developed for genital arousal disorders.

Results of survey

Zero people responded to the survey distributed via professional medical associations and available on the project website. A separate survey was distributed by the Nurse Practitioners in Women's Health (NPWH) organization; 96 people responded to this survey (refer to Table 11 for respondent characteristics and Appendix 2.2 for survey instrument).

Among respondents, 3 (3%) used oxytocin in combination with sildenafil citrate or tadalafil as a compounded drug. Respondents used oxytocin in combination with sildenafil citrate or tadalafil as an oral or sublingual troche (2, 67% of respondents) and oxytocin alone as an oral troche (1, 33%). Respondents used oxytocin in combination with sildenafil citrate or tadalafil to increase female orgasm intensity (2, 67%); 1 respondent (33%) selected 'other' for the condition or disease for which they prescribed oxytocin in combination with sildenafil citrate or tadalafil, but provided no further explanation (refer to Table 12).

The 3 respondents used compounded oxytocin in combination with sildenafil citrate or tadalafil due to lack of commercial products in an appropriate dosage form, strength or combination (33% of 3 responses), patient allergies (0%), other patient conditions preventing use of commercial products (33%), or no commercially available products with oxytocin in combination with sildenafil citrate or tadalafil (0%) (refer to Table 13). One (33%) respondent selected 'other' for reason for using compounded oxytocin in combination with sildenafil citrate or tadalafil but provided no further explanation.

The majority of respondents who used compounded oxytocin in combination with sildenafil citrate or tadalafil (2, 67%) did not stock non-patient-specific these products at their practice. Respondents obtained compounded oxytocin in combination with sildenafil citrate or tadalafil by compounding the products themselves at their practice (1, 33% of 3 responses), having the product compounded at an in-house pharmacy (1, 33%), or other with no explanation (1, 33%). Refer to Table 14 for how respondents obtained compounded oxytocin in combination with sildenafil citrate or tadalafil.

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	**Responses, n (N=96)[a]**
Doctor of Medicine (MD)	0
Doctor of Osteopathic Medicine (DO)	0
Doctor of Medicine in Dentistry (DMD/DDS)	0
Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)	0
Master of Science (MS)	1
Naturopathic Doctor (ND)	0
Nurse Practitioner (NP)	95
Physician Assistant (PA)	0
Practice Setting	**Responses, n (N=96)[a]**
Physician office or private practice	47
Outpatient clinic	29
Hospital or health system	9
Academic medical center	7
Emergency room	0
Operating room	1
Other[b]	3

[a]Some respondents reported more than one terminal clinical degree and/or practice setting.
[b]Responses to other: retired from research; Graduate Education Program faculty; "recently moved to FL."

Table 12. Conditions for which oxytocin in combination with sildenafil or tadalafil prescribed

Condition	Responses, n (N=3)[a]
Increase female orgasm intensity	2
Induction of labor	0
Postpartum hemorrhage	0
Adjunct for induced abortion	0
Other[b]	1

[a]Out of 96 respondents, 3 reported prescribing or using compounded oxytocin in combination with sildenafil citrate or tadalafil.
[b]No explanation provided for 'other'.

Table 13. Reasons for using compounded oxytocin in combination with sildenafil or tadalafil

Reason	Responses, n (N=3)[a]
Commercial product not available in desired dosage form, strength or combination	1
Patient allergies prevent use of commercial products	0
Patient conditions prevent use of commercial products	1
No commercial products	0
Other[b]	1

[a]Out of 96 respondents, 3 reported prescribing or using compounded oxytocin in combination with sildenafil citrate or tadalafil.
[b]No explanation provided for 'other'.

Table 14. Use of non-patient-specific compounded oxytocin in combination with sildenafil or tadalafil

Do you stock non-patient-specific compounded oxytocin in combination with sildenafil citrate or tadalafil at your practice?	**Responses, n (N=3)[a]**
Yes	1
No	2
Not sure	0
How do you obtain compounded oxytocin in combination with sildenafil citrate or tadalafil?	
Compound yourself at practice	1
Product compounded by in-house pharmacy	1
Purchase from compounding pharmacy	0
Purchase from outsourcing facility	0
Other[b]	1

[a]Out of 96 respondents, 3 reported prescribing or using compounded oxytocin in combination with sildenafil citrate or tadalafil.
[b]No explanation provided for 'other'.

CONCLUSION

Sildenafil citrate was nominated for inclusion on the 503B Bulks List as nominated for ED via an oral/sublingual troche combined with oxytocin. Sildenafil citrate is not available in the nominated dosage form and ROA in the US or any of the national medical registries searched.

From the literature review and interviews conducted, sildenafil citrate is one of the FDA-approved PDE5Is used for management of ED. The current ED treatment options involve a PDE5I medication, Trimix injection, or penile implant. None of the SMEs had used the nominated combination of oxytocin with sildenafil citrate as an oral or sublingual troche, and there were no studies found describing this combination. A couple SMEs stated there is potential value of having this combination around (given it is effective) as an alternative for patients in which sildenafil is not working and who do not want to use injections. One SME used oxytocin as a 250 units lozenge that patients (man or woman) take 1 hour before sex and stated that oxytocin either works well or not at all. For men, this SME prescribes oxytocin with sildenafil and tadalafil, but not as a combination product. Another factor to consider is the oral bioavailability of oxytocin because it is a peptide.

Zero people responded to the survey distributed via professional medical associations and available on the project website. From the NPWH survey responses, 3 out of 96 respondents used compounded oxytocin in combination with sildenafil citrate or tadalafil. The most common indication respondents used compounded oxytocin in combination with sildenafil citrate or tadalafil for was to increase female orgasm intensity. Lack of commercial products in an appropriate dosage form, strength or combination and patient conditions preventing the use of commercially available products were some of the reasons for using compounded oxytocin in combination with sildenafil citrate or tadalafil product over an FDA-approved product. One respondent reported stocking compounded oxytocin in combination with sildenafil citrate or tadalafil in at their practice.

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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 April 9, 2020
- Date last searched: April 10, 2020
- Limits: Humans (search hedge); English language
- Number of results: 12
- Note: One search constructed for three nominated substances, oxytocin, sildenafil citrate and tadalafil, because sildenafil citrate and tadalafil only nominated for oral/sublingual use in combination with oxytocin

1	oxytocin/	19533
2	ox#tocin$.tw.	22858
3	oc#tocin$.tw.	89
4	or/1-3	27690
5	administration, oral/	141269
6	administration, sublingual/	2930
7	oral$.tw.	658787
8	sublingual$.tw.	10818
9	lozenge?.tw.	1112
10	troche?.tw.	163
11	or/5-10	707908
12	exp erectile dysfunction/	18862
13	orgasm/	2367
14	(erect$ adj2 (dysfunction$ or function$)).tw.	18683
15	impoten$.tw.	6712
16	orgasm$.tw.	3852
17	((sex or sexual$) adj2 (activit$ or arous$ or disorder$ or dysfunction$ or function$ or gratif$ or hypoactiv$ or problem$ or satisf$ or symptom$)).tw.	48208
18	sildenafil/	5333

19	tadalafil/	1371
20	sildefil$.tw.	0
21	sildenafil$.tw.	6497
22	tadalafil$.tw.	1956
23	or/12-22	77307
24	and/4,11,23	12
25	exp animals/ not humans/	4689197
26	24 not 25	12
27	limit 26 to english language	12

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: April 10, 2020
- Limits: Humans (search hedge); English language
- Number of results: 34
- Note: One search constructed for three nominated substances, oxytocin, sildenafil citrate and tadalafil, because sildenafil citrate and tadalafil only nominated for oral/sublingual use in combination with oxytocin

1	oxytocin'/de	36690
2	oxytocin':ti,ab,tn	28572
3	oxitocin*':ti,ab,tn	86
4	ocytocin*':ti,ab,tn	125
5	ocitocin*':ti,ab,tn	6
6	#1 OR #2 OR #3 OR #4 OR #5	42016
7	sublingual drug administration'/de	4483
8	oral drug administration'/de	404866
9	lozenge'/de	1188
10	sublingual*':ti,ab	16170
11	oral*':ti,ab	946822
12	lozenge$':ti,ab	1524
13	troche$':ti,ab	244
14	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	1243823
15	sexual dysfunction'/exp	86847
16	orgasm'/de	6258
17	(erect* NEAR/2 (dysfunction* OR function*)):ti,ab	30597
18	impoten*':ti,ab	9537
19	orgasm*':ti,ab	6982
20	((sex OR sexual) NEAR/2 (activit* OR arous* OR disorder* OR dysfunction* OR function* OR gratif* OR hypoactiv* OR problem* OR satisf* OR symptom*)):ti,ab	71725

21	sildenafil'/de	21304
22	tadalafil'/de	6810
23	sildefil*':ti,ab,tn	0
24	sildenafil*':ti,ab,tn	10195
25	tadalafil*':ti,ab,tn	3319
26	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	156198
27	#6 AND #14 AND #26	40
28	[animals]/lim NOT [humans]/lim	6014039
29	#27 NOT #28	39
30	#27 NOT #28 AND [english]/lim	34

Appendix 2.1. Survey instrument for professional medical associations

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

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

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

Thank you,

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

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

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

1. How familiar are you with the following terms?

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

2. Which of the following do you prescribe or administer to your patients? (check all that apply)

   - ○ Oxytocin alone
   - ○ Oxytocin/sildenafil citrate
   - ○ Oxytocin/tadalafil
   - ○ None of the above

3. Do you prescribe or administer single-agent oxytocin and/or multi-ingredient oxytocin products by any of the following dosage forms and/or routes of administration? (check all that apply)

   - ○ Oral troche
   - ○ Sublingual troche
   - ○ None of the above

4. I prescribe or administer single-agent oxytocin and/or multi-ingredient oxytocin products for the following conditions or diseases: (check all that apply)

   - ○ Erectile dysfunction
   - ○ Increase orgasm intensity
   - ○ Other (please explain) _____

5. I use compounded single-agent oxytocin and/or multi-ingredient oxytocin products because: (check all that apply)

    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain)_____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing single-agent oxytocin and/or multi-ingredient oxytocin products.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded single-agent oxytocin and/or multi-ingredient oxytocin products at your practice?

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

7. I obtain compounded single-agent oxytocin and/or multi-ingredient oxytocin products from the following: (check all that apply)

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

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

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

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

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

Appendix 2.2. Survey instrument for Nurse Practitioners in Women's Health

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

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

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

Thank you,

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

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

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

1. How familiar are you with the following terms?

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

2. Do you utilize a 503B outsourcing facility to acquire compounded drugs?
    - ○ Yes. If yes, why? _____
    - ○ No. If no, why not? _____

3. Which of the following compounded drugs do you prescribe or administer to your patients? (please check all that apply)
    - ○ Alprostadil as a solo product
    - ○ Alprostadil/Papaverine/Phentolamine as a combination product
    - ○ Aminophylline
    - ○ Anastrozole as a solo product
    - ○ Anastrozole/Testosterone as a combination product
    - ○ Oxytocin in combination with sildenafil citrate or tadalafil
    - ○ None of the above

4. Do you prescribe or administer alprostadil as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - ○ Topical cream, lotion, gel and/or solution
    - ○ Other (please explain) _____
    - ○ None of the above

5. I prescribe or administer alprostadil as a single agent product for the following conditions or diseases: (please check all that apply)
    - ○ Female sexual arousal disorder
    - ○ Other (please explain) _____
    - ○ None of the above

6. I use compounded alprostadil as a single agent product because: (please check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - Patient allergies prevent me from using commercially available products. (please explain) _____
    - Patient conditions prevent me from using commercially available products. (please explain) _____
    - There are no commercially available products containing alprostadil.
    - Other (please explain) _____
7. Do you stock non-patient-specific compounded alprostadil as a single agent product at your practice?
    - Yes
    - No
    - I'm not sure
8. I obtain compounded alprostadil as a single agent product from the following: (please check all that apply)
    - Compound myself at my practice
    - Have the product compounded by an in-house pharmacy
    - Purchase, or have a patient purchase, from a compounding pharmacy
    - Purchase, or have a patient purchase, from an outsourcing facility
    - Other (please explain) _____
9. Do you prescribe or administer alprostadil / papaverine / phentolamine as a combination product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - Topical cream, lotion, gel and/or solution
    - Other (please explain) _____
    - None of the above
10. I prescribe or administer alprostadil / papaverine / phentolamine as a combination product for the following conditions or diseases: (please check all that apply)
    - Female sexual arousal disorder
    - Other (please explain) _____
    - None of the above
11. I use compounded alprostadil / papaverine / phentolamine as a combination product because: (please check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - Patient allergies prevent me from using commercially available products. (please explain) _____
    - Patient conditions prevent me from using commercially available products. (please explain) _____
    - There are no commercially available products containing alprostadil / papaverine / phentolamine.
    - Other (please explain) _____

12. Do you stock non-patient-specific compounded alprostadil / papaverine / phentolamine as a combination product at your practice?
    - Yes
    - No
    - I'm not sure
13. I obtain compounded alprostadil / papaverine / phentolamine as a combination product from the following: (please check all that apply)
    - Compound myself at my practice
    - Have the product compounded by an in-house pharmacy
    - Purchase, or have a patient purchase, from a compounding pharmacy
    - Purchase, or have a patient purchase, from an outsourcing facility
    - Other (please explain) _____
14. Do you prescribe or administer aminophylline as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - IV injection
    - Oral liquid
    - Oral capsules
    - Topical cream, gel and/or ointments
    - Other (please explain) _____
    - None of the above
15. I prescribe or administer aminophylline as a single agent product for the following conditions or diseases: (please check all that apply)
    - Orgasmic dysfunction
    - Other (please explain) _____
    - None of the above
16. I use compounded aminophylline as a single agent product because: (please check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - Patient allergies prevent me from using commercially available products. (please explain) _____
    - Patient conditions prevent me from using commercially available products. (please explain) _____
    - There are no commercially available products containing aminophylline.
    - Other (please explain) _____
17. Do you stock non-patient-specific compounded aminophylline as a single agent product at your practice?
    - Yes
    - No
    - I'm not sure

18. I obtain compounded aminophylline as a single agent product from the following: (please check all that apply)
    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____
19. Do you prescribe or administer anastrozole as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Subcutaneous or subdermal pellet
    - o Other (please explain) _____
    - o None of the above
20. I prescribe or administer anastrozole as a single agent product for the following conditions or diseases: (please check all that apply)
    - o Hormone replacement
    - o Other (please explain) _____
    - o None of the above
21. I use compounded anastrozole as a single agent product because: (please check all that apply)
    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing anastrozole.
    - o Other (please explain) _____
22. Do you stock non-patient-specific compounded anastrozole as a single agent product at your practice?
    - o Yes
    - o No
    - o I'm not sure
23. I obtain compounded anastrozole as a single agent product from the following: (please check all that apply)
    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____
24. Do you prescribe or administer anastrozole / testosterone as a combination product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Subcutaneous or subdermal pellet
    - o Other (please explain) _____
    - o None of the above

25. I prescribe or administer anastrozole / testosterone as a combination product for the following conditions or diseases: (please check all that apply)
    - o Hormone replacement
    - o Other (please explain) _____
    - o None of the above
26. I use compounded anastrozole / testosterone as a combination product because: (please check all that apply)
    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing anastrozole / testosterone.
    - o Other (please explain) _____
27. Do you stock non-patient-specific compounded anastrozole / testosterone as a combination product at your practice?
    - o Yes
    - o No
    - o I'm not sure
28. I obtain compounded anastrozole / testosterone as a combination product from the following: (please check all that apply)
    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____
29. Do you prescribe or administer oxytocin with sildenafil citrate or tadalafil as a combination product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Oral or sublingual troche
    - o Intravenous or intramuscular injection
    - o Other (please explain) _____
30. I prescribe or administer oxytocin with sildenafil citrate or tadalafil as a combination product for the following conditions or diseases: (please check all that apply)
    - o Increase female orgasm intensity
    - o Induction of labor
    - o Postpartum hemorrhage
    - o Adjunct for induced abortion
    - o Other (please explain) _____

31. I use compounded oxytocin with sildenafil citrate or tadalafil as a combination product because: (please check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - Patient allergies prevent me from using commercially available products. (please explain) _____
    - Patient conditions prevent me from using commercially available products. (please explain) _____
    - There are no commercially available products containing oxytocin with sildenafil citrate or tadalafil.
    - Other (please explain) _____
32. Do you stock non-patient-specific compounded oxytocin with sildenafil citrate or tadalafil as a combination product at your practice?
    - Yes
    - No
    - I'm not sure
33. I obtain compounded oxytocin with sildenafil citrate or tadalafil as a combination product from the following: (please check all that apply)
    - Compound myself at my practice
    - Have the product compounded by an in-house pharmacy
    - Purchase, or have a patient purchase, from a compounding pharmacy
    - Purchase, or have a patient purchase, from an outsourcing facility
    - Other (please explain) _____
34. 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 explain) _____
35. What degree do you hold? (please check all that apply)
    - Nurse Practitioner (NP)
    - Other (please explain) _____

Appendix 3. Survey distribution to professional associations

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

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

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

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