Summary Report

Estradiol

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

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REVIEW OF NOMINATIONS

Estradiol (UNII code: 4TI98Z838E) was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society and Rebecca Mitchell for moderate to severe menopause related symptoms (abnormal vasomotor function, atrophic vulva, atrophy of vagina, and urethral atrophy), prophylaxis of postmenopausal osteoporosis, metastatic breast cancer and advanced androgen-dependent prostate carcinoma (for palliation only), and decreased estrogen level secondary to hypogonadism, castration, or primary ovarian failure. The nominated formulation is a subcutaneous implantable pellet with strengths ranging from 6-75 mg per pellet.

Reasons given for nomination to 503B Bulks List are as follows:

- There are no commercially available products that include estradiol as an implantable pellet.
- 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 more safe and 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.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of estradiol 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 (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 estradiol; name variations of estradiol 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(s); strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROAs 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 estradiol. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

Two databases (PubMed and Embase) were searched including any date through April 10, 2019. The search included a combination of (estradiol[TIAB] OR oestradiol[TIAB]) AND (pellet OR implant) AND (humans[MeSH Terms] AND English[lang]) NOT autism. Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

Study selection

Literature reviews and/or meta-analyses, cost-effectiveness, and epidemiological studies were excluded. Estradiol is a component of an FDA-approved product. As a result, articles were excluded if estradiol was utilized as the FDA-approved product or in the same concentration and formulation as the FDA-approved product. Additional exclusion criteria included any dosage form/ROA that differed from the nominated dosage form/ROA. Articles were considered relevant based on the identification of a clinical use of estradiol or the implementation of estradiol 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.

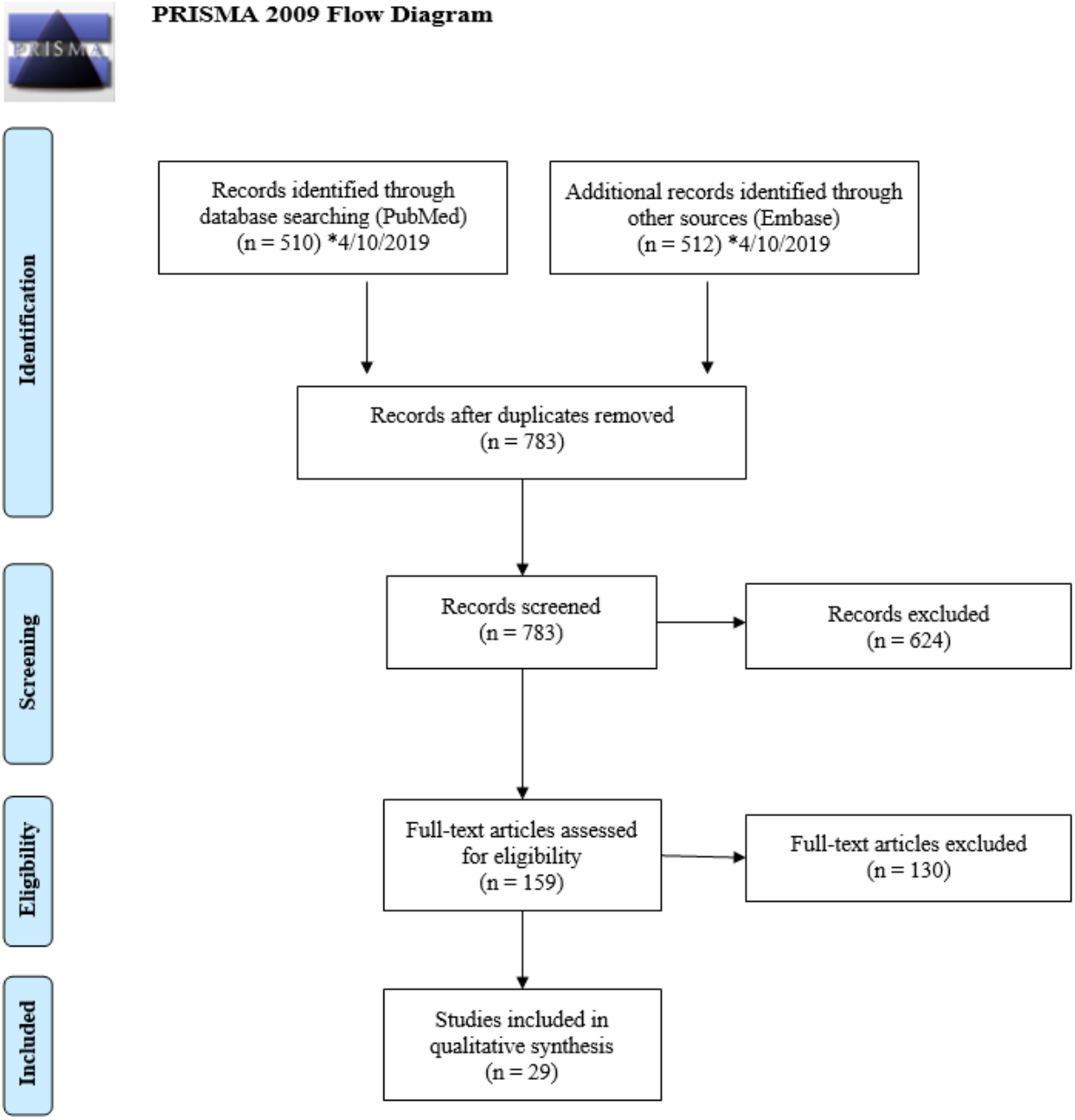
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for estradiol 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 estradiol 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, six (6) medical specialties that would potentially use estradiol were identified: endocrinology, naturopathy, obstetrics and gynecology, oncology, primary care, and urology. 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. Two (2) experts were contacted for interviews, of which two (2) accepted and zero (0) declined interviews. One (1) interview was recorded and transcribed via ©Rev.com, while the other was not recorded due to equipment failure. QSR International's Nvivo 12 software was utilized for qualitative data analysis. The University of Maryland, Baltimore IRB and the Food & Drug Administration (FDA) 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 endocrinology, naturopathy, obstetrics and gynecology, oncology, primary care, and urology, identified from the nominations, 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.

The online surveys were created using Qualtrics® software (Provo, UT). Survey links were distributed to ten 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.

Estradiol was included on two (2) surveys distributed to the associations in Table 1. Due to the identification of additional substances relevant to these associations, estradiol was included on surveys with dehydroepiandrosterone (DHEA), estradiol cypionate, estriol, estrone, medroxyprogesterone, pregnenolone, progesterone, testosterone, testosterone cypionate, and testosterone propionate.

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
Naturopathy	American Association of Naturopathic Physicians (AANP)
Primary care	American Academy of Environmental Medicine (AAEM)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Endocrinology	American Association of Clinical Endocrinologists (AACE)	Declined, "endocrinologists are not generally in the compounding space"
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Obstetrics and Gynecology	American College of Obstetricians and Gynecologists (ACOG)	Declined, survey not approved for distribution.
Oncology	American Society of Clinical Oncology (ASCO)	Failed to respond
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond
Urology	American Urology Association (AUA)	Declined, "our physicians are inundated with surveys and I'm afraid you won't be able to get the information you need"

CURRENT AND HISTORIC USE

Summary of background information

- Estradiol is not available as an FDA-approved product.
- Estradiol is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for estradiol.
- Estradiol is not available in any of the foreign medicine registries searched.

Table 3. Currently approved products – US

No approved products in the US

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

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

Summary of literature review

- Total number of studies included: 29 studies (3 descriptive, 20 experimental, and 6 observational studies).
- Most of the studies were from the UK (20 studies).
- The most common indication for the use of estradiol in the US was prostatic cancer. The most common indications from the non-US studies were menopausal symptoms and osteoporosis/bone loss prevention in menopause.
- No compounded products were identified from any studies.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[1-3]	3
Experimental[4-23]	20
Observational[24-29]	6

Table 6. Number of studies by country

Country	Number of Studies
Brazil[4,24]	2
Israel[18]	1
UK[1,5-11,13-17,19-23,27,28]	20
US[2,3,12,25,26,29]	6
	Total US: 6 Total non-US Countries: 23

Table 7. Number of studies by combinations

No combination products were nominated

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Prostatic carcinoma[3,12,29]	25-50mg/3 months	25mg	Pellet	Subcutaneous	–
In vitro fertilization[26]	100-250mg	25mg	Pellet	Subcutaneous	Once
Prevention of premature menopause[2]	50-200mg/6-12 months	–	Implant	Subcutaneous	–
Surgical menopause[25]	25-75mg	25mg	Pellet	–	–

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

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Menopausal symptoms[4,5-8,10,11,19,20]	25-75mg/6 months	50mg	Implant	–	3 years
	80-100mcg	–		Subdermal	1 year
	50mg/4-12 months	50mg		Subcutaneous	2 months - 4 years
Osteoporosis/bone loss prevention in menopause[9,14,17,21,23,24,27,28]	40-200mg/year	20-50mg	Implant	Percutaneous, subcutaneous	0.5-22 years
Depressive symptoms[1,11]	25-100mg/6 months	100mg	Implant	–	8 years
Premenstrual syndrome[11,15]	25-100mg/7 days-6 months	100mg	Implant	Subcutaneous	10 months
Contraception[18]	25mg/year	25mg	Pellet	Subcutaneous	2-10 years
Endometriosis after hysterectomy[16]	50mg/6 months	50mg	Implant	–	3.7 years
Prevention of vasomotor symptoms in hysterectomy patients[13]	100mg	100mg	Implant	–	–
Overactive bladder[23]	25mg	25mg	Implant	Subcutaneous	–

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

Table 10. Compounded products – US

No compounded products from reported studies

Table 11. Compounded products – non-US countries

No compounded products from reported studies

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

Two (2) interviews were conducted. For one interview, the audio recording did not function.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Estradiol	Interview Summary Response
END_01	MD	Internal Medicine Endocrinology and Metabolism	Academic medical institution	Yes	• Does not stock in office • Concerns with office stock • Uses FDA approved products, exceptions usually due to cost
OBG_01	MD	Obstetrics and Gynecology	Academic medical institution	Yes	• Concerned about compounded products and sees decreased need for them

Abbreviation: MD, Doctor of Medicine.

Office stock:

- Neither interviewee expressed a need for office stock.
- One interviewee had concerns with most doctors not being set up to have office stock, and the issue of patients/staff taking the stock out without permission.

Compounding estradiol:

- Difficult to compound
  - One interviewee stated, "one of the biggest concerns that we have is that we think that compounded estradiol…oral and topical progesterone with estradiol…are difficult to compound."
- Decreased need due to more available FDA products
  - One interviewee stated,"…we have FDA-approved Estradiol as an oral, a patch, a gel, a spray, a lotion, a ring, as well as vaginal products…We have vaginal Estrogen available as a cream - both brand and generic, tablet - both brand and generic, new suppositories,…And then we have a new oral Estradiol Progesterone combination that just came out…the change between 2002 and now is that we have a very large number of FDA approved Estradiol and Progesterone options that meet the criteria of bioidentical,…and they're also available in a wide variety of doses…So it means that the number of people who need to have compounded bioidentical hormone therapy has decreased."
  - For back order issues, one interviewee expressed, "…when we get a back order issue, and we ran into one of these this past year, I believe that it was maybe EstroGel that was on back order. But then we could switch people to a similar dose of

Divigel or Oestrogel. If we have somebody who has a patch allergy, it used to be that, that meant that we needed to go to something compounded, but we don't need to do that now because we have so many different brand names."

- Compounding estradiol pellets:
  - An interviewee expressed concern about compounding estradiol pellets: "…my understanding with the pellets is that they are a high dose, and a sustained dose. And so from the point of view of being easy for providers to insert them and not having to think about taking something on a daily or twice weekly basis. There might be some benefit but there is major concern in the medical community about these high doses and whether or not they may be increasing the risk for breast cancer or uterine cancer."
- Cost:
  - Previously, providers used compounding pharmacies for lower cost but now there are generics available.
  - Both interviewees usually use FDA-approved products. One exception might be because of cost.

Supplemental Information

- One interviewee provided references regarding the serious health and safety risks associated with the use of compounded "bioidentical" hormone products in menopausal women, as well as scientific, positional statements, and other publicly available documents nominating hormones that are demonstrably difficult to compound.[30-40]
  - The nominated hormones for inclusion on the demonstrably difficult to compound list includes bio-identical hormones in the pellet form, estradiol in the oral and topical dosage forms and estradiol with progesterone also in the oral and topical dosage forms.[34,40]
  - Estradiol is a highly potent molecule with low aqueous solubility.[39,40]
  - There is concern estradiol will not be uniformly distributed within the mixture.[40]
  - There are numerous FDA-approved bioidentical hormone therapies available including estrogen (estradiol, estrone), progesterone, and an oral estradiol/progesterone product in late stage development.[35,38,39,40]

Summary of survey results

Table 13. Characteristics of survey respondents [59 people responded to survey.[a]]

Board Certification	MD	ND	NP	No Response
Endocrinology, Diabetes and Metabolism	0	1	0	0
Family Medicine	1	0	1	0
Fellow of the American Board of Naturopathic Oncology	0	1	0	0
Integrative Medicine	2	0	0	0
Naturopathic Doctor	0	6	0	0
Naturopathic Physician	0	9	0	0
Obstetrics and Gynecology	2	0	0	0
Thoracic Surgery	1	0	0	0
No Board Certification	1	4	0	0
No Response	0	0	0	39

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

[a]Some respondents reported more than one terminal clinical degree or board certification.

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

Types of Products	Respondents, n (N=51[a])
Compounded	19[b]
FDA-approved	10
Over-the-counter	1
Dietary	1
Unsure	0
No response	31

[a]Out of 59 respondents, 51 reported using, prescribing, or recommending multiple types of estradiol product.
[b]14 respondents used in combination (see Figure 2 below for specifics)

Figure 2. Compounded combinations reported in the survey

Active ingredients in combination products:

- Estradiol, estriol ("Bi Est" or "Biest")
- Estradiol, estriol, progesterone
- Estradiol, estriol, progesterone, testosterone
- Estradiol, progesterone
- Estradiol, progesterone, testosterone
- Estradiol, testosterone
- Estradiol, testosterone, dehydroepiandrosterone (DHEA)

Forms of combination products:

- Cream
- Tablet
- Troche
- Topical, form not specified

Table 15. Compounded use of estradiol in practice[a,b]

Indication	Strength	Dosing frequency	Dosage Form	ROA	Duration of Treatment	Patient Population
Menopause[c]	12.5-50mg	Every 4-6 months	Pellets	Subcutaneous	3 months – 8+ years As needed Long-term Varies	Dyspareunia on low dose BCPs Female 30+ years old Polycystic ovary patients
	"0.25 mg/gtt"	Daily	Tincture	Sublingual		
	Variable		Troche			
	"1.5mg/g"	Daily	"1 click"	Topical		
	0.1-1mg		Cream			
	0.5-2mg/mL					
	Variable	Daily	"Topical"	Transdermal		
	"0.05-0.1 patch"	Every 3.5 days	Patch			
	0.10-0.25mg	Daily	Tablet	Vaginal		
	0.1-4mg	Daily	Cream	Transdermal, vaginal		
	0.5 mg	Daily	–	Sublingual, topical, "IM vaginal"		
	0.025mg-8mg/day	2x/week to twice daily	Cream, patch, suppositories, troches	Oral, transdermal, vaginal		
	0.375mg, 1mg, 6mg, 10mg	2x/week-daily	Cream, patch, pellet	–		
	6-25mg	Every 3 months - Daily	Pellet	–		

	0.5-1mg	Daily	Cream	–		
Menstrual migraines	0.025-0.05mg	1-2x/month	Patch, troche	Oral, transdermal	"Short-term, long-term, intermittent/PRN"	Premenopausal females
Atrophic vaginitis	0.5-2 mg	Daily	Cream	Vaginal	Long-term	Post menopausal
Premature ovarian failure	1.25mg	"Daily for 2 weeks, then stop"	Cream	Vagina/labia	3-6 months	Females 20-35
Premature ovarian insufficiency	0.025mg-8mg/day	2x/week to twice daily	Cream, patch, suppositories, troches	Oral, transdermal, vaginal	Short-term or Long-term	Female (35+)
"Hormone balance"	–	–	–	–	–	–

Abbreviations: "–", not mentioned; ROA, route of administration.
[a]14 respondents
[b]Quotations are direct words from respondents.
[c]Includes perimenopause; menopausal symptoms and conditions such as hot flashes, dryness, osteoporosis/osteopenia, insomnia and vaginitis.

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

Indication	Standard Therapy			
	Compounded, n (N=19)	Non-compounded, n (N=12)	Unsure, n (N=0)	No response, n (N=31)
Menopause[b]	11	0	0	0
No standard	1	0	0	0
Pre-mature ovarian insufficiency	1	0	0	0
Transgenderism	1	0	0	0
Vaginal atrophy with pain, painful sex	1	0	0	0
No response	6	1	0	31

[a]Some respondents reported more than one indication.
[b]Includes perimenopause; menopausal symptoms and conditions such as hot flashes, dryness, osteoporosis/osteopenia, insomnia and vaginitis.

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

Theme	Reasons
Cost	• "Cost is less expensive--same chemical (estradiol)"
Safety	• "It is a safer product that is much easier to dose and is less risky than the estrogens from horses that are not the same molecule as human estrogen." • "I use both. Some women have adverse effects from binders, dyes, etc. used in approved drugs." • "Absence of synthetic additives/preservatives, patient preference" • "Compounded is pure, we know ingredients, the compounding pharmacists are trained in natural therapies, like us, so working together is a no-brainer !!" • "I trust that compounded pharmacies are making pure products and correct dosages "
Versatility	• "Versatility in dosing and route of admin" • "Ability to titrate dose to need" • "Ability to combine therapies in one form." • "I use FDA-approved patches if patient desires, but prefer compounded product to create natural rhythm for healthier outcomes (no FDA product available)" • "I use low dose to ultra low doses" • "Personalized and precision dosing, mode of administration" • "Ability to customize dose as well as combine it with estriol and other hormones" • "Need more than limited dosing options" • "Not enough dose, cost, inability to combine with other hormones, lack of choice, only a few dosages, can't individualize treatment"

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

	Respondents, n (N=19)
No - use has remained consistent	8
Yes - I use it LESS often now	1
Yes - I use it MORE often now • "Research even more supportive of benefits" • "Seeing more patients for menopausal issues" • "Adding to the Progesterone product" • "I trust that compounded pharmacies are making pure products and correct dosages" • "The need is great and FDA drugs aren't adequate dose or delivery systems"	5
No response	5

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

	Respondents, n (N=19)
No	13
Yes[a]	1
No response	5

[a]One (1) respondent reported stocking non-patient specific compounded estradiol in the physician office, and purchased from a compound pharmacy for convenience and emergencies. The respondent also explained that pellets are often dropped during the insertion process and must be replaced immediately and that they change the dose at the time of visit.

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

No additional survey respondents provided information for this section

CONCLUSION

Estradiol (UNII code: 4TI98Z838E) was nominated for inclusion on the 503B Bulks List mor moderate to severe menopause related symptoms (abnormal vasomotor function, atrophic vulva, atrophy of vagina, and urethral atrophy), prophylaxis of postmenopausal osteoporosis, metastatic breast cancer and advanced androgen-dependent prostate carcinoma (for palliation only), and decreased estrogen level secondary to hypogonadism, castration, or primary ovarian failure. The nominated formulation is a subcutaneous implantable pellet with various strengths ranging from 6-75 mg per pellet. Estradiol is not approved in any of the foreign medicine registries searched.

From the literature review conducted, the most common indication in the US was prostatic cancer. The most common indications from the non-US studies were menopausal symptoms and osteoporosis/bone loss prevention in menopause. No compounded products were identified from any studies.

From the interviews, both interviewees preferred FDA-approved estradiol products over compounded estradiol products with some exceptions such as cost. Specifically for compounding estradiol pellets, one interviewee expressed concern about possible high doses from the pellets since providers can just insert the pellet and not have to think about it as often as with a daily or weekly product. High doses can increase the risk for breast cancer or uterine cancer.

From the survey responses, 51 out of 59 respondents used estradiol. The most common indication respondents used compounded estradiol for was menopause and/or menopausal symptoms. Cost, safety, and versatility were some of the reasons for using the compounded estradiol product over an FDA-approved product. One (1) respondent reported stocking compounded estradiol in the physician office.

APPENDICES

Appendix 1. References

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Appendix 2. Survey instrument

Estradiol

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 **estradiol**. 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: Estradiol

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

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

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Display This Question:

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

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

Display This Question:

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

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

_____

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

_____

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

_____

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

- ○ Yes - I use it **MORE** often now (briefly describe why)_____
- ○ Yes - I use it **LESS** often now (briefly describe why)_____
- ○ No - use has remained consistent

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

_____

Q9 Do you stock non-patient-specific compounded **estradiol** in your practice location?

- ○ Yes
- ○ No

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

Display This Question:

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

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

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

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

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

_____

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

_____

End of Block: Estradiol

Start of Block: Background Information

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

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

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

- [ ] No Board certification
- [ ] Allergy and Immunology
- [ ] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [ ] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology

- ☐ Neurology
- ☐ Obstetrics and Gynecology
- ☐ Oncology
- ☐ Ophthalmology
- ☐ Otolaryngology
- ☐ Pain Medicine
- ☐ Pediatrics
- ☐ Psychiatry
- ☐ Rheumatology
- ☐ Sleep Medicine
- ☐ Surgery (please describe) _____
- ☐ Urology
- ☐ Other (please describe)_____

End of Block: Background Information