Summary Report

Estradiol cypionate

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:

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

December 2019

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.

Table of Contents

Table of Tables

REVIEW OF NOMINATIONS

Estradiol cypionate (UNII code: 7E1DV054LO) was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society (SSPS) and Rebecca Mitchell for abnormal vasomotor function (moderate to severe) due to menopause and "decreased estrogen level – female hypogonadism syndrome" via a 5 mg/mL intramuscular preserved solution (oil).

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

- Manufacturer backorder.
- When a different strength or dosage form is required.
- 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 cypionate 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 cypionate; name variations of estradiol cypionate 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 cypionate. 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

Estradiol cypionate is a component of an FDA-approved product. The desired compounded products identified in the submitted nominations do not substantially differ from the commercially available product. Therefore, a systematic literature review was not completed.

Outreach to medical specialists and specialty organizations

Using the indications from the nominations, four (4) medical specialties that would potentially use estradiol cypionate were identified: endocrinology, naturopathy, obstetrics and gynecology, and primary care. 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 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 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, and primary care, 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 eight (8) 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 cypionate 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 cypionate was included on surveys with dehydroepiandrosterone (DHEA), estradiol, 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
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

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

Table 3. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	ROA	Status	Approval Date[b]
Estradiol cypionate	5mg/mL	Injectable	Injection	Prescription	Approved prior to 01/01/1982

Abbreviation: ROA, route of administration.
[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

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

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

Summary of literature review

No literature review was conducted.

Table 5. Types of studies

No literature review was conducted

Table 6. Number of studies by country

No literature review was conducted

Table 7. Number of studies by combinations

No literature review was conducted

Table 8. Dosage by indication – US

No literature review was conducted

Table 9. Dosage by indication – non-US countries

No literature review was conducted

Table 10. Compounded products – US

No literature review was conducted

Table 11. Compounded products – non-US countries

No literature review was conducted

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 Cypionate	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, Medical Doctor

Office stock:

- Both interviewees did not express the need for office stock.
- One interviewee had concerns with most doctors not being set up to have it and there could also the issue of patients/staff taking the stock out without permission.

Compounding estradiol cypionate:

- Both interviewees did not specifically express needing to have estradiol cypionate compounded
- One interviewee has not given estradiol cypionate in doses higher than 5 mg or used it in combination that may have warranted needing estradiol cypionate to be compounded.

General thoughts on compounded hormone products:

- Decreased need due to more available FDA products
- 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
- 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”

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 norminating hormones that are demonstrably difficult to compound.[1-11]
  - The references provided information regarding estradiol. However, there was no specific information regarding estradiol cypionate for intramuscular use

Summary of survey results

Table 13. Characteristics of survey respondents [53 people responded to survey.[a]]

Board Certification	MD	ND	No Response
Endocrinology, Diabetes and Metabolism	0	1	0
Fellow of the American Board of Naturopathic Oncology	0	1	0
Naturopathic Doctor	0	6	0
Naturopathic Physician	0	9	0
No Board Certification	1	4	0
No Response	0	0	38

Abbreviations: MD, Doctor of Medicine; ND, Naturopathic Doctor

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

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

Types of Products	Respondents, n (N=7[a])
Compounded	1
FDA-approved	0
Over-the-counter	0
Dietary	0
No response	6

[a]Out of 53 respondents, 7 reported using, prescribing, or recommending multiple types of estradiol cypionate product

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

Indication	Strength	Dosing frequency[b]	Dosage Form	ROA	Duration of treatment	Patient population
Menopausal symptoms in women who have hysterectomies, menopausal women	5mg/mL	"1 time every 4-5 weeks"	Injectable	Intramuscular	As long as needed	Females

Abbreviation: ROA, route of administration.
[a]One (1) respondent
[b]Quotations are direct words from respondents

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

Indication	Standard Therapy			
	Compounded, n (N=1)	Non-compounded, n (N=0)	Unsure, n (N=0)	No response, n (N=6)
Menopause, surgical menopause	1	0	0	0
No response	0	0	0	6

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

Theme	Reasons
Cost	• "Less expensive"

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

	Respondents, n (N=1)
No - use has remained consistent	1
Yes - I use it LESS often now	0
Yes - I use it MORE often now	0

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

	Respondents, n (N=1)
No	1
Yes	0

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

No survey respondents provided information for this section

CONCLUSION

Estradiol cypionate (UNII code: 7E1DV054LO) was nominated for inclusion on the 503B Bulks List for abnormal vasomotor function (moderate to severe) due to menopause and "decreased estrogen level – female hypogonadism syndrome" via a 5 mg/mL intramuscular preserved solution (oil). Estradiol cypionate is FDA approved as an injection and is not available in any of the foreign medicine registries searched. No literature review was conducted.

From the interviews, neither interviewee specifically expressed the need to compound estradiol cypionate. From the survey results, seven (7) respondents selected that they use estradiol cypionate and one (1) responded using compounded 5 mg/mL estradiol cypionate intramuscularly for menopausal symptoms. A reason provided for using compounded product instead of the FDA-approved products is that it is less expensive.

APPENDICES

Appendix 1. References

1. Citizen petition from TherapeuticsMD, Inc. *Food and Drug Administration.* 2018. https://www.regulations.gov/document?D=FDA-2018-P-4714-0001. Published December 12, 2018. Accessed November 27, 2019.
2. Archer D. Nomination from David Archer. *Food and Drug Administration.* 2018. https://www.regulations.gov/document?D=FDA-2017-N-2562-0016. Published October 9, 2018. Accessed November 22. 2019.
3. Davis SR, Baber R, Panay N, et al. Global consensus position statement on the use of testosterone therapy for women. *J Sex Med.* 2019;16(9):1331-1337.
4. Develen C. Comment from Carolyn Develen. *Food and Drug Administration Notice: Drug Products That Present Demonstrable Difficulties for Compounding Under the Federal Food, Drug, and Cosmetic Act.* 2018. https://www.regulations.gov/document?D=FDA-2017-N-2562-0017. Published October 9, 2018. Accessed November 27, 2019.
5. Endocrine Society. Comment from Endocrine Society. *Food and Drug Administration Notice: Drug Products That Present Demonstrable Difficulties for Compounding Under the Federal Food, Drug, and Cosmetic Act.* 2017. https://www.regulations.gov/document?D=FDA-2017-N-2562-0006. Published December 14, 2017. Accessed November 22, 2019.
6. Endocrine Society. Compounded bioidentical hormone therapy. *An Endocrine Society Position Statement.* 2019. https://www.endocrine.org/news-and-advocacy/position-statements/compounded-bioidentical-hormone-therapy. Published October 2, 2019. Accessed November 27, 2019.
7. Pinkerton J, Sánchez Aguirre F, Blake J, et al. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause.* 2017;24(7):728-753.
8. Pinkerton JV, Conner EA, Kaunitz AM. Management of menopause and the role For hormone therapy. *Clin Obstet Gynecol.* 2019;62(4):677-686.
9. Santoro N, Braunstein GD, Butts CL, Martin KA, McDermott M, Pinkerton JV. Compounded bioidentical hormones in endocrinology practice: an Endocrine Society scientific statement. *J Clin Endocrinol Metab.* 2016;101(4):1318-1343.
10. Stamoran C. Comment from Catalent Applied Drug Delivery Institute. *Food and Drug Administration Notice: Drug Products That Present Demonstrable Difficulties for Compounding Under the Federal Food, Drug, and Cosmetic Act.* 2018. https://www.regulations.gov/document?D=FDA-2017-N-2562-0011. Published May 7, 2018. Accessed November 27, 2019.
11. Utian W. Comment from Wulf Utian. *Food and Drug Administration (FDA) Proposed Rule: Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act.* 2014. https://www.regulations.gov/document?D=FDA-2013-N-1523-0036. Published July 8, 2014. Accessed November 22, 2019.

Appendix 2. Survey instrument

Estradiol cypionate

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 cypionate**. 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 cypionate

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

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

---

Display This Question:

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

Q2 Please list any conditions or diseases for which you use compounded **estradiol cypionate** 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 cypionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- ☐ Single
- ☐ Combination

Skip To: Q6 If Do you use compounded estradiol cypionate as a single agent active ingredient, or as one active i... != Combination

Display This Question:

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

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

_____

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

_____

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

_____

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

_____

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

- ○ Yes
- ○ No

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

Display This Question:

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

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

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

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

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

_____

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

_____

End of Block: Estradiol cypionate

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