



September 24, 2025

Submitted via <https://www.regulations.gov/document/FDA-2025-N-2589-0001/comment>.

Martin A. Makary, MD, MPH
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Docket No. FDA-2025-N-2589, FDA Expert Panel on Menopause and Hormone Replacement Therapy for Women

Dear Commissioner Makary:

The Society for Women's Health Research (SWHR) appreciates the opportunity to provide comments in response to the U.S. Food and Drug Administration (FDA) Expert Panel on Menopause and Hormone Replacement Therapy for Women (Docket No. FDA-2025-N-2589). Founded in 1990, SWHR is a national nonprofit dedicated to advancing women's health through science, policy, and education, while promoting research on sex differences to optimize women's health. We are committed to translating scientific evidence into policies and practice to improve treatment outcomes and ensure that patients have access to safe and effective therapies.

Approximately 1.3 million women transition into menopause each year in the United States, and 85% of midlife women report experiencing varying symptoms and degrees of severity.^{1,2} SWHR continues to emphasize the need for access to a comprehensive range of treatments and interventions to assist women during this life stage.

SWHR applauds the FDA's commitment to addressing the health needs of midlife and older women. As the FDA considers how local, vaginal estrogen products are labeled, SWHR asks the following to be considered:

Evidence-Based Safety and Efficacy of Vaginal Estrogen

Scientific literature supports the safety and efficacy of vaginal estrogen for women experiencing a range of symptoms and conditions during and post-menopause. It has long been considered a first-line therapy for the treatment of moderate-to-severe genitourinary syndrome of menopause (GSM).³ GSM, a collection of vulvovaginal and lower urinary tract symptoms, including dryness; burning, painful intercourse; and recurrent urinary tract infections (UTIs), resulting

¹ Takahashi TA, Johnson KM. Menopause. *Med Clin North Am.* 2015;99(3):521-534. doi: 10.1016/j.mcna.2015.01.006

² McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Maturitas.* 1992;14(2):103-115. doi:10.1016/0378-5122(92)90003-m

³ Da Silva AS, Baines G, Araklitis G, Robinson D, Cardozo L. Modern management of genitourinary syndrome of menopause. *Fac Rev.* 2021;10:25. doi:10.12703/r/10-25

from the decline of estrogen.⁴ A recent 2021 meta-analysis asserted that vaginal estrogen significantly lowers the risk of UTIs and their recurrence, offering a strong preventive option.^{5,6}

Additionally, multiple high-quality studies have addressed breast cancer risk, recurrence, and mortality concerns. A cohort study of 50,000 breast cancer survivors found no increase in early breast cancer-specific mortality among vaginal estrogen users.⁷ Similarly, a 2025 meta-analysis found no association between vaginal estrogen and recurrence, cancer-specific mortality or overall mortality.⁸ Collectively, the evidence underscores the safety and efficacy of low-dose vaginal estrogen treatment that alleviates menopause symptoms without compromising breast cancer outcomes.

Consensus by Leading Medical Societies

Prominent medical societies, such as The Menopause Society (TMS), American College of Obstetricians and Gynecologists (ACOG), American Urological Association (AUA), International Society for the Study of Women's Sexual Health (ISSWSH), and the Endocrine Society, agree that local, low-dose vaginal estrogen is safe and effective, including for women with a history of breast cancer when non-hormonal options are insufficient.^{9,10,11} The 2025 updated guidelines from AUA, Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU), and American Urogynecologic Society (AUGS) also specifically endorse the use of local, low-dose vaginal estrogen as a first-line therapy for GSM relief.¹²

Harms of Current Labeling and Black Box Warning

The FDA's current black box warning on local vaginal estrogen fails to reflect the robust evidence regarding the safety and efficacy of low-dose, local therapies. The warning placed on local vaginal estrogen products has led to clinical and patient barriers, resulting in women suffering despite having treatable symptoms. Although evidence supporting its safety is widely published and known, physicians remain hesitant to prescribe low-dose vaginal estrogen therapy due to outdated safety concerns and limited menopause training, significantly influencing

⁴ Kim HK, Kang SY, Chung YJ, Kim JH, Kim MR. The recent review of the genitourinary syndrome of menopause. *J Menopausal Med.* 2015;21(2):65-71. doi:10.6118/jmm.2015.21.2.65

⁵ Chen YY, Su TH, Lau HH. Estrogen for the prevention of recurrent urinary tract infections in postmenopausal women: a meta-analysis of randomized controlled trials. *Int Urogynecol J.* 2021;32(1):17-25. doi:10.1007/s00192-020-04397-z

⁶ Meister MR, Wang C, Lowder JL, Mysorekar IU. Vaginal estrogen therapy is associated with decreased inflammatory response in postmenopausal women with recurrent urinary tract infections. *Female Pelvic Med Reconstr Surg.* 2021;27(1):e39-e44. doi:10.1097/SPV.0000000000000790

⁷ McVicker L, Labeit AM, Coupland CA, et al. Vaginal estrogen therapy use and survival in females with breast cancer. *JAMA Oncol.* 2024;10(1):103-108. doi: 10.1001/jamaoncol.2023.4508

⁸ Beste ME, Kaunitz AM, McKinney JA, Sanchez-Ramos L. Vaginal estrogen use in breast cancer survivors: a systematic review and meta-analysis of recurrence and mortality risks. *Am J Obstet Gynecol.* 2025;232(3):262-270.e1. doi:10.1016/j.ajog.2024.10.054

⁹ Faubion SS, Crandall CJ, Davis L, et al. The 2022 hormone therapy position statement of the North American Menopause Society. *Menopause.* 2022;29(7):767-794. doi:10.1097/GME.0000000000002028

¹⁰ ACOG Committee Opinion No. 659: The use of vaginal estrogen in women with a history of estrogen-dependent breast cancer. *Obstet Gynecol.* 2016;127(3):e93-e96. doi:10.1097/AOG.0000000000001351

¹¹ Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2015;100(11):3975-4011. doi:10.1210/jc.2015-2236

¹² Kaufman MR, Ackerman AL, Amin KA, et al. The AUA/SUFU/AUGS guideline on genitourinary syndrome of menopause. *J Urol.* 2025;214(3):242-250. doi:10.1097/JU.0000000000004589

prescribing patterns and restricting patient access to this form of treatment.¹³ Hormone safety misconceptions and health education gaps among providers and patients leave many women unaware of the benefits of vaginal estrogen for conditions like GSM; these challenges contribute to major barriers in treatment initiation and adherence and undermine confidence among both parties.^{14,15,16} Physicians must be better equipped to discuss the risks and benefits of vaginal hormone therapy with their patients, particularly with those who have not found relief using non-hormonal alternatives.

Millions of women suffer unnecessarily when effective, evidence-based treatment options exist but are underutilized due to stigma and overly broad warnings. A shift in this paradigm, led by the FDA, will help reshape perceptions of estrogen-based hormone therapies during menopause.

Recommendations

SWHR urges the FDA to:

1. **Update Product Labeling:** Remove or revise the black box warning for local vaginal estrogen to reflect the latest scientific evidence in a clear and accessible manner.
2. **Advance Patient Education:** Leverage the FDA Office of Women's Health and leading midlife health stakeholders to develop accessible educational resources for women and providers on treatment options for GSM, including vaginal local estrogen.
3. **Promote Shared Decision-Making:** Recommend using language on boxed and class warnings that encourages revisiting decisions with an individual's clinician if their health status changes and avoid overstating systemic risks for low-dose vaginal estrogen to minimize unnecessary alarm.

SWHR appreciates the FDA's commitment to supporting women's health by opening this issue up for public comment and working to address the needs of midlife women.

If you have questions or would like to discuss these comments further, please contact SWHR Chief Advocacy Officer Lindsey Miltenberger at 202-496-5003 or via email at lindsey@swhr.org

¹³ Rozenberg S, Panay N, Gambacciani M, Cano A, Gray S, Schaudig K. Breaking down barriers for prescribing and using hormone therapy for the treatment of menopausal symptoms: an experts' perspective. *Expert Rev Clin Pharmacol*. 2023;16(6):507-517. doi: 10.1080/17512433.2023.2219056

¹⁴ Kingsberg SA, Schaffir J, Faught BM, et al. Female sexual health: barriers to optimal outcomes and a roadmap for improved patient-clinician communications. *J Womens Health (Larchmt)*. 2019;28(4):432-443. doi:10.1089/jwh.2018.7352

¹⁵ Kingsberg SA, Larkin L, Krychman M, Parish SJ, Bernick B, Mirkin S. WISDOM survey: attitudes and behaviors of physicians toward vulvar and vaginal atrophy treatment in women including those with breast cancer history. *Menopause*. 2019;26(2):124-131. doi:10.1097/GME.0000000000001194

¹⁶ Nappi RE, Palacios S, Bruyniks N, Particco M, Panay N; EVES Study Investigators. The burden of vulvovaginal atrophy on women's daily living: implications on quality of life from a face-to-face real-life survey. *Menopause*. 2019;26(5):485-491. doi:10.1097/GME.0000000000001260