ETHICS AND PUBLIC POLICY CENTER

June 17, 2026

The Commissioner of Food and Drugs
c/o Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Citizen Petition Pursuant to 21 C.F.R. § 10.30 Requesting the FDA (A) Open a Docket, (B) Hold a Part 15 Public Hearing Regarding the Off-Label Use of Estrogen in Natal Males for Gender Affirmation, and (C) Consider Regulatory Action Including a Boxed Warning Under 21 C.F.R. § 201.80(e)

Dear Commissioner:

We are scholars at the Ethics and Public Policy Center, where our initiatives—the Person and Identity Project (PIP) and the Administrative State Accountability Project (ASAP)—engage research, policy, and regulations related to the "gender dysphoria" diagnosis and sex-rejecting procedures,[1] including the off-label use of estrogen in males. We write to the U.S. Food and Drug Administration (FDA) in support of the "Citizen Petition Pursuant to 21 C.F.R. § 10.30 Requesting the FDA (A) Open a Docket, (B) Hold a Part 15 Public Hearing Regarding the Off-Label Use of Estrogen in Natal Males for Gender Affirmation, and (C) Consider Regulatory Action Including a Boxed Warning Under 21 C.F.R. § 201.80(e)."[2]

PIP and ASAP, as well as other scholars at EPPC, have been tracking the growing evidence of immediate and long-term harm from the use of estrogen in males who reject their sex

[1] *Cf.* Eric Kniffin, Mary Hasson & Rachel N. Morrison, Terminology and Definition: Replacing "Gender-Affirming Care" with "Sex-Rejecting Procedures," EPPC (May 2, 2025),https://eppc.org/wp-content/uploads/2025/09/Replacement-Term-for-GAC.pdf (proposing the term "sex-rejecting procedures" as a replacement for "gender-affirming care" and other terms for "medical procedures connected with a so-called 'gender transition'"); Press Release, Dep't of Health & Hum. Servs. (HHS), HHS Acts to Bar Hospitals from Performing Sex-Rejecting Procedures on Children (Dec. 18, 2025), https://www.hhs.gov/press-room/hhs-acts-bar-hospitals-performing-sex-rejecting-procedures-children.html (using the term "sex-rejecting procedures" to discuss medical interventions for gender dysphoria, including puberty-suppressing hormones, cross-sex hormones, and surgical procedures); Off. of the Sec'y, HHS, Declaration Re: Safety, Effectiveness, and Professional Standards of Care for Sex-Rejecting Procedures on Children and Adolescents (Dec. 18, 2025) (defining "sex- rejecting procedures" as "pharmaceutical or surgical interventions, including puberty blockers, cross-sex hormones, and surgeries such as mastectomies, vaginoplasties, and other procedures, that attempt to align an individual's physical appearance or body with an asserted identity that differs from the individual's sex").

[2] Citizen Petition Requesting Regulatory Action on the Off-Label Use of Estrogen in Natal Males, Docket No. FDA-2025-P-7321 (Dec. 17, 2025), https://www.regulations.gov/document/FDA-2025-P-7321-0001.

and / or self-identify as "transgender" or another chosen ("non-male") identity. These males use estrogen in supra-physiologic doses, typically in combination with androgen suppressants,[3] for sex-rejecting purposes—that is, to alter the appearance of the male body to appear less identifiably male and to disable the healthy functioning of the male reproductive system. As discussed below, the claim that current "standards" and protocols govern the use of estrogen in males, and therefore have a protective effect, is specious. The supposed "standards" and protocols are not evidence-based, and value individual wish fulfillment over evidence and safety. Further, the use of estrogen in males for sex-rejecting purposes has some significant harmful effects. However, the lack of research, coupled with poor-quality research, raises significant concerns about unknown risks and unknown long-term effects.

We urge the FDA to grant the petition and: (a) conduct a review of the adverse events associated with off-label use of estrogen in males who reject their sex and / or self-identify as "transgender" or another chosen ("non-male") identity; (b) hold a public hearing regarding this important issue; and (c) consider regulatory action, including issuing a black box warning based on research to date, alerting the public (especially potential users) of the significant harms and risks associated with the use of estrogen in males.

A. The claim that existing "standards" and protocols safely guide off-label estrogen use by males is specious.

The off-label use of estrogen for sex-rejecting purposes (often misleadingly described as "gender-affirming care") is purportedly governed by "several protocols" set by the World Professional Association for Transgender Health (WPATH) "Standards of Care" (SOC 8) and by the Endocrine Society guidelines.[4] According to WPATH, "'[g]ender diversity is a natural variation in people and is not inherently pathological.' However, no evidence is presented" to support WPATH's viewpoint, and WPATH cites its own prior statements for authority.[5] Further, "the quality of evidence" supporting those protocols is low, and "optimal target ranges have not been established for serum sex steroids levels."[6] In fact, WPATH is an activist organization and its "Standards" have been thoroughly discredited because they reflect ideological bias and are not grounded in reliable evidence.[7] The Endocrine Society's clinical practice guideline, which

[3] "Treatment with physiologic doses of estrogen alone is insufficient to suppress testosterone levels into the normal range for cisgender females. Therefore, individuals undergoing feminizing hormone therapy require the addition of an anti-androgen medication to further inhibit testosterone signaling either by inhibiting production or by blocking the androgen receptor. In the USA, all forms of estradiol (parenteral, oral, and patches or gels) are combined with androgen suppressive therapy, usually spironolactone." Spironolactone carries risks, particularly the risk of hyperkalemia (high potassium with potential serious effects). Inder Sehgal, *Review of Adult Gender Transition Medications: Mechanisms, Efficacy Measures, and Pharmacogenomic Considerations*, 14 Frontiers in Endocrinology 1184024 (2023) (as corrected Jan. 6, 2025), https://pmc.ncbi.nlm.nih.gov/articles/PMC10355117/.

[4] *Id.*

[5] Andrew Amos, *The Gender-Affirming Model of Care Is Incompatible with Competent, Ethical Medical Practice*, 32 Australasian Psychiatry 220 (2024), https://pmc.ncbi.nlm.nih.gov/articles/PMC11103900/.

[6] *Id.*

[7] Chloe K. Jones, *The Façade of Medical Consensus: How Medical Associations Prioritize Politics over Science*, Harv. J.L. & Pub. Pol'y (June 3, 2025), https://journals.law.harvard.edu/jlpp/the-facade-of-medical-consensus-chloe-jones/; *see also, generally*, HHS, Treatment for Pediatric Gender Dysphoria: Review of Evidence and Best Practices (Nov. 19, 2025), https://opa.hhs.gov/sites/default/files/2025-11/gender-dysphoria-report.pdf.

recommends the off-label use of estrogen in males for sex-rejecting purposes—despite little supporting evidence—was co-authored by WPATH-affiliated physicians.[8] It too fails to meet criteria for evidence-based guidelines.[9] These "protocols" fail to provide reliable clinical guidance and are inadequate to ensure the safety of males who use estrogen for sex-rejecting purposes. In short, neither WPATH "standards" nor Endocrine Society protocols safely guide off-label estrogen use in males.

B. Off-label estrogen use in males has significant harmful effects.

Despite the overall lack of quality evidence to support the off-label use of estrogen in males, a growing body of research demonstrates that this use poses significant risks to health and psychological wellbeing, with additional unknown, long-term health risks.

For example, infertility has long been recognized as a risk associated with the use of supraphysiological doses of estrogen in males for sex-rejecting purposes.[10] Studies have found that males on estrogen experience testicular atrophy and numerous "sperm abnormalities," which can result in temporary or permanently impaired fertility.[11] Further, no studies have assessed the "long-term health outcomes and quality of life of children born by the use of gametes preserved" after male exposure to supraphysiological doses of estrogen."[12] The negative effects of estrogen use in males may be generational—a consequence that should raise alarm but is rarely considered.

Estrogen use for sex-rejecting purposes in males increases the risk of cardiovascular issues, strokes, and blood clots. For instance, a "narrative review concluded there was 'strong evidence that estrogen therapy for trans women [males] increases their risk for venous thromboembolism [VTE] over fivefold."[13] And "a large cohort study following 2517 transgender women [males] for an average of about 9 years reported a standardized incidence ratio (SIR) for VTE" over four times higher in transgender-identified males using estrogen compared to other males.[14] VTE risks measured over longer periods were even higher.[15] Stroke risks for males

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[8] Wylie C. Hembree et al., *Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline*, 102 J. Clin. Endocrinol. & Metab. 3869 (2017).

[9] "The WPATH and Endocrine Society international guidelines … lack developmental rigour and transparency" and "[t]he two guidelines also have close links, with WPATH adopting Endocrine Society recommendations in its own guideline and acting as a cosponsor for and providing input on drafts of the Endocrine Society guideline." Jo Taylor et al., *Clinical Guidelines for Children and Adolescents Experiencing Gender Dysphoria or Incongruence: A Systematic Review of Guideline Quality (Part 1)*, 109 Archives of Disease in Childhood s65 (2024), https://adc.bmj.com/content/109/Suppl_2/s65.

[10] Lauren Schwartz et al., *Emerging and Accumulating Safety Signals for the Use of Estrogen Among Transgender Women*, 5 Discover Mental Health 88 (2025), https://pmc.ncbi.nlm.nih.gov/articles/PMC12162459/.

[11] *Id.*

[12] C. De Roo et al., *Fertility in Transgender and Gender Diverse People: Systematic Review of the Effects of Gender-Affirming Hormones on Reproductive Organs and Fertility*, 31 Human Reproduction Update 183 (2025), https://pubmed.ncbi.nlm.nih.gov/39854640/.

[13] Schwartz, et al. (2025).

[14] *Id.*

[15] *Id.*

using estrogen have been reported to be 30% higher than for other males, and "nearly 10 times higher after 6 years."[16]

Metabolic dysfunction is an additional concern. One study reports that diabetes in males who use estrogen for sex-rejecting purposes is more prevalent than diabetes in women, although similar to other males.[17] However, a systematic review found that "estradiol, with or without anti-androgen, decreases lean mass, increases fat mass, and may worsen insulin resistance," all of which have been linked to increased diabetes risk.[18]

Puberty blockers (GnRH analogs), which are often used prior to or even along with the introduction of estrogen in males for sex-rejecting purposes, suppresses bone mineralization and may affect overall bone growth. The off-label use of estrogen in males may improve bone mineralization scores, post-puberty blockers, but still be "insufficient to optimize BMD [bone mineral density]" depending on dosage.[19]

Other debilitating conditions linked to the use of estrogen in males for sex-rejecting purposes include severe and worsening headaches,[20] increased risks of developing multiple sclerosis,[21] heightened risk of thyroid cancer,[22] and potentially higher risks of breast cancer.[23]

It is important to note, however, that the harms go beyond physical consequences. A young man who uses supraphysiological doses of estrogen to alter his body, in hopes of relieving identity-related distress or escaping his hated male anatomy, may worsen his disassociation from the body and consequently suffer greater distress and other psychological disturbances. Estrogen itself "induces changes in the brain, raising concerns for negative impacts on mood (e.g., depression) and cognition."[24]

Relatedly, the off-label use of estrogen in males can impair sexual function, causing "diminished libido, sexual dysfunction, and loss of spontaneous erections,"[25] and worsen

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[16] *Id*.

[17] Noreen Islam et al., *Is There a Link Between Hormone Use and Diabetes Incidence in Transgender People? Data from the STRONG Cohort*, 107 J. Clin. Endocrinol. & Metab. e1549 (2022), https://doi.org/10.1210/clinem/dgab832.

[18] C. Spanos et al., *Effects of Gender-Affirming Hormone Therapy on Insulin Resistance and Body Composition in Transgender Individuals: A Systematic Review*, 11 World J. Diabetes 66 (2020); P. Panday et al., *Incidence of Type 2 Diabetes Mellitus in Transgender Individuals Undergoing Gender Affirming Hormonal Therapy: A Systematic Review*, 16 Cureus e58137 (2024), https://pmc.ncbi.nlm.nih.gov/articles/PMC11088936/.

[19] L.S. Boogers et al., *The Dose-Dependent Effect of Estrogen on Bone Mineral Density in Trans Girls*, Eur. J. Endocrinol. (advance access pub. 2023), https://academic.oup.com/ejendo/advance-article/doi/10.1093/ejendo/lvad116/7244658.

[20] L.J. Zavala et al., *Headache in Individuals Undergoing Hormone Therapy for Gender Transition: A Cross-Sectional, Observational Study*, 66 Headache 725 (2026), https://pubmed.ncbi.nlm.nih.gov/41103036/.

[21] J. Pakpoor et al., *Gender Identity Disorders and Multiple Sclerosis Risk: A National Record-Linkage Study*, 22 Multiple Sclerosis J. 1759 (2016).

[22] J.D. Christensen et al., *Thyroid Cancer Prevalence, Risk Exposure, and Clinical Features Among Transgender Female Veterans*, 8 J. Endocrine Soc'y art. bvae060 (2024), https://pmc.ncbi.nlm.nih.gov/articles/PMC11023629/.

[23] Schwartz et al. (2025).

[24] *Id.*

[25] Hembree et al. (2017).

psychological distress. Studies also report conflicting findings about the impact of high-dose estrogen in males on cognition, although one study links estrogen use to impaired "information-processing speed and episodic memory."[26]

Finally, consistent evidence over time has found higher "all-cause mortality risk" in males using sex-rejecting hormones, compared to the general population.[27] Research over five decades showed "[c]ause-specific mortality in transgender women [males] was high for cardiovascular disease, lung cancer, HIV-related disease, and suicide," and the "increased mortality risk did not decrease over time."[28]

No evidence supports the claim that providing males with high-dose estrogen for sex-rejecting purposes is beneficial; indeed, the evidence to date suggests the opposite. Off-label use of high-dose estrogen in otherwise healthy males disables healthy development, impairs healthy organ and endocrine functions, and results in demonstrable physical harm.

C. Research on off-label estrogen use in males is lacking and its long-term effects are unknown.

Evaluating the use of estrogen in males for sex-rejecting purposes is complicated by the poor quality of research in this area. Studies suffer from a range of weaknesses, including:

- Use of observational or retrospective studies (which cannot determine causality);
- Variable sample sizes and inconsistent inclusion criteria;
- Short follow-up periods (few longitudinal studies);
- High rates of loss to follow-up (shrinking sample sizes over time);
- Lack of standardized outcome measures (no consensus on appropriate measures); and
- Failure to assess and control for confounding factors (e.g., dosage differences, varied means of hormone administration, age variance within and across samples, prior health concerns, and co-occurring mental health issues).

Further, existing research—in addition to being generally low quality—neglects significant areas of medical concern. For example, "there are nutrition-relevant conditions that may concomitantly occur with GAHT ["gender-affirming hormone therapy," i.e., the use of sex-rejecting hormones]" such as "insulin resistance, diabetes, dyslipidemia, hypertension, and other biochemical alterations."[29] Nutrition standards are sex-specific, however, so their application is unclear, and the use of sex-rejecting hormones results in "changes in certain biochemical measures over time," but the meaning of those changes is unclear.[30] Clinicians receive little guidance on how to interpret those changes. Overall, "research on the biochemical impact of … feminizing hormone therapy is nascent and limited. Methodologies and outcomes measured are

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[26] Schwartz et al. (2025).

[27] C.J. de Blok et al., *Mortality Trends over Five Decades in Adult Transgender People Receiving Hormone Treatment: A Report from the Amsterdam Cohort of Gender Dysphoria*, 9 Lancet Diabetes & Endocrinol. 663 (2021); Schwartz et al. (2025).

[28] *Id*.

[29] J. Waters & W. Linsenmeyer, *The Impact of Gender-Affirming Hormone Therapy on Nutrition-Relevant Biochemical Measures*, 11 Frontiers in Nutrition 1339311 (2024), https://pubmed.ncbi.nlm.nih.gov/38646103/.

[30] *Id*.

heterogenous across studies, introducing complexities that impede researchers from drawing definitive conclusions."[31]

Similarly, little evidence exists to guide clinicians' use of laboratory tests or the laboratories' selection of appropriate "reference ranges," which are critically important measures that detect and signal a wide range of physical pathologies, including endocrine abnormalities, metabolic disorders, prostate cancer, and other health concerns.[32] Off-label estrogen use in males for sex-rejecting purposes also may result in misleading test results for kidney function, with consequent "misdiagnosis or misclassification of kidney disease stages."[33]

Although the use of estrogen in identity-distressed males has been justified by claims that these sex-rejecting interventions reduce the risk of suicide, no credible evidence supports those claims; nor is there any evidence that denying the use of sex-rejecting hormones in transgender-identified males results in greater suicide risks.[34]

D. The FDA should act to address these concerns.

In sum, there is no ethical, medical purpose for prescribing estrogen as a treatment for males who experience identity distress, reject their male sex, or self-identify as transgender. Males who identify as transgender currently are subject to intense social media campaigns that encourage them to use estrogen for sex-rejecting purposes, with little to no understanding of immediate and long-term harms that may result. By providing sex-rejecting hormones (high doses of estrogen) to troubled young males, physicians and gender clinics sabotage the efforts of family and friends seeking to help the young person embrace the healthy reality of his body and sexual identity. Indeed, in the absence of a black box warning, parents, siblings, and friends who express concern over potential side effects of estrogen use in males for sex-rejecting purposes are likely to be sidelined or silenced by pro-gender ideology advocates and organizations. Honest discussion of the harms of these sex-rejecting interventions is too often stifled.

For these reasons, we urge the FDA (a) to conduct a serious investigation into the harms of using supraphysiological doses of estrogen for sex-rejecting purposes in males, (b) to hold a public hearing into their use and effects, and (c) to require a black box warning regarding the use of estrogen in males for sex-rejecting purposes. Further, given the known harms of off-label use of estrogen in males for sex-rejecting purposes, we urge the FDA to issue a black box warning immediately, so that the public receives timely warning during the pendency of the recommended rigorous investigation, rather than waiting for its completion.

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[31] *Id.*

[32] I. Ramasamy, *Gender Reassignment and the Role of the Laboratory in Monitoring Gender-Affirming Hormone Therapy*, 13 J. Clinical Med. 5134 (2024), https://pubmed.ncbi.nlm.nih.gov/39274346/.

[33] P. Reema et al., *Kidney Health and Gender-Affirming Hormone Therapy for Transgender and Gender Diverse Individuals*, 21 Clin. J. Am. Soc'y Nephrology 154 (2026), https://pmc.ncbi.nlm.nih.gov/articles/PMC13135061/.

[34]Michael Biggs, Comment on Jack Turban et al., *Access to Gender-Affirming Hormones During Adolescence and Mental Health Outcomes Among Transgender Adults*, PLoS One (Jan. 19, 2022), https://journals.plos.org/plosone/article/comment?id=10.1371/annotation/dcc6a58e-592a-49d4-9b65-ff65df2aa8f6.

Conclusion

The FDA should grant the petition.

Sincerely,

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