December 17, 2025

*[Submitted Electronically]*

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

**CITIZEN PETITION**

**Subject: 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)**

## I. ACTION REQUESTED

The undersigned petitioners, representing a coalition of clinicians, researchers, affected individuals, and public health stakeholders, submit this Citizen Petition under 21 C.F.R. § 10.30. We are concerned by the dramatic increase in the off-label use of estrogen in natal males for the purpose of altering secondary sex characteristics to affirm a gender identity inconsistent with their natal sex. The recent peer-reviewed umbrella review from the Department of Health and Human Services has once again demonstrated the lack of benefits from these hormonal interventions. What is perhaps less appreciated is the increasing evidence of *harm*.

We are asking the Food and Drug Administration (FDA) to fulfill its public health mission by promoting awareness of the state of evidence concerning this use, which is off-label, and by alerting manufacturers and healthcare providers that, because this use is unapproved, it is unlawful to promote it—directly or indirectly. This is needed to raise public awareness of the long-term risks and outcomes associated with the use of estrogen in natal males for the purpose of modifying secondary sex characteristics, as this use has not been shown to be safe, and to prevent further harm to these individuals. Additionally, there is a lack of substantial evidence that estrogen improves psychosocial well-being in natal males.

We request that the FDA take the following immediate actions regarding the widespread, off-label use of estrogen-containing pharmaceutical products (including but not limited to formulations of estradiol, estradiol esters, and conjugated estrogens) administered systemically to males for the purpose of altering secondary sex characteristics to affirm a gender identity inconsistent with their natal sex (hereafter referred to as "off-label use of estrogen in natal males"):

- **Open a New, Dedicated Public Docket:** Establish a distinct public docket specifically

focused on the safety and effectiveness of this off-label use of estrogen in natal males. This docket will serve as a central repository for scientific evidence, clinical experience, patient testimony, and public comment necessary for a thorough regulatory evaluation.

- **Convene a Part 15 Public Hearing:** Schedule and conduct a public hearing pursuant to 21 C.F.R. Part 15 to gather testimony and information from scientific experts, medical practitioners, patients (including detransitioners), ethicists, and the public regarding the risks, potential benefits, and scientific uncertainties associated with this off-label use.

## RECOMMENDATIONS

Furthermore, based on the substantial evidence presented herein demonstrating that this off-label use meets the criteria specified in 21 C.F.R. § 201.80(e), we urge the FDA, following the establishment of the docket and the conclusion of the Part 15 hearing, to consider the following recommendations for further regulatory actions necessary to protect public health. Recommended actions include, but are not limited to:

- **Mandate a Boxed Warning:** Require a boxed warning on the labeling of all relevant estrogen-containing products detailing the specific, severe risks associated with their off-label use in natal males for gender affirmation, consistent with the authority under 21 C.F.R. § 201.80(e).

- **Conduct a Comprehensive Safety Review & REMS Evaluation:** Initiate a formal, comprehensive review of the safety data for this off-label use, potentially leading to the implementation or modification of Risk Evaluation and Mitigation Strategies (REMS) to ensure any potential benefits outweigh the risks.

- **Mandate Enhanced Adverse Event Reporting:** In addition to a robust REMS, establish a formal system for rigorous post-market surveillance of this off-label use, issue guidance to clinicians on their obligation to report all serious adverse events to the FDA Adverse Event Reporting System (FAERS), and require manufacturers to establish a patient registry as part of a REMS to capture real-world safety data.

- **Develop Communications for Medical Providers:** Such communications would include the following:

    - Mandatory documentation of informed consent and capacity assessment prior to initiating treatment in adolescents and vulnerable adults. As we detail under Section B, "Specific Concerns for Vulnerable Populations," the prevalence rate of Autism Spectrum Disorder (ASD) in this population is more than seven times higher than the rate of 3.2% in the general youth population—a rate that the HHS has recently called a 'rampant epidemic.'
    - Required evaluation of coexisting psychiatric or neurodevelopmental factors (including Autism Spectrum Disorder, psychiatric comorbidities, or trauma history) that may affect understanding of the short- and long-term implications of medical transition.

- A comprehensive, multidisciplinary assessment for coexisting mental health concerns that may interfere with diagnostic clarity, capacity to consent, or the gender-affirming process should be well-controlled before any medical intervention is initiated.
- Requirement for fertility-preservation informed consent before initiation of treatment, as mentioned in the Endocrine Society guidelines.
- Recommendation that prescribers obtain a licensed mental-health professional's assessment when decisional capacity or diagnostic clarity is uncertain.

This petition addresses a critical regulatory gap concerning this off-label use of powerful hormonal drugs in a growing and vulnerable population, often without adequate evidence, oversight, or fully informed consent. The requested actions are necessary to align regulatory practice with emerging scientific evidence and the fundamental principle of patient safety.

## II. STATEMENT OF GROUNDS

This petition addresses the safety of estrogen and its ineffectiveness on psychosocial outcomes, despite its frequent use as the second step in an off-label medical pathway for natal males who seek modification of secondary sex characteristics. Due to the overlap in population, many of our concerns align with the concerns detailed in a pending Citizen Petition (Docket FDA-2023-P-3767) filed on September 1, 2023, and supplemented on April 15, 2024, which addressed the first step in this pathway: the off-label use of GnRH agonists (puberty blockers).

The FDA possesses the authority under 21 C.F.R. § 201.80(e) to mandate specific warnings, including boxed warnings, for common off-label uses of approved drugs that lack substantial evidence of effectiveness and are associated with serious risk or hazard. This off-label use of estrogen in natal males unequivocally meets all three requisite conditions stipulated in this regulation.

### A. Off-label use of estrogen in males for the purpose of modifying secondary sex characteristics is associated with serious risk or hazard.

The off-label use of estrogen in natal males is associated with a wide spectrum of severe, well-documented risks across multiple organ systems. Crucially, these safety signals cannot be viewed in isolation. While individual adverse event rates for conditions such as venous thromboembolism, stroke, or malignancy may appear as distinct probabilities, the aggregate probability that a patient will suffer at least one serious adverse outcome increases significantly when multiple systems are impacted simultaneously. This cumulative burden likely explains the alarming mortality data observed in long-term cohorts.

These risks often accumulate over time and meet the threshold of "special problems, particularly those that may lead to death or serious injury," justifying consideration of a boxed warning under 21 C.F.R. § 201.80(e). Evidence synthesized by Schwartz et al., 2025 and

supplemented by other sources includes:

- **Profound Cardiovascular and Thromboembolic Harm:**
    - **Venous Thromboembolism (VTE)**: The risk increases 5.1-fold after 2 years compared to the general male population (Getahun et al., 2018).
    - **Stroke**: The risk increases nearly 10-fold after 6 years (Getahun et al., 2018).
    - **Retinal Vein Occlusion**: Case reports link estrogen therapy to branch retinal vein occlusion (BRVO), a cause of sudden vision loss (Andzembe et al., 2023).
- **Significant Oncologic Risk:**
    - **Breast Cancer**: The standardized incidence ratio (SIR) increases 22.5- to 40.7-fold compared to the general population of males (Corso et al., 2023).
    - **Testicular Cancer**: Annual incidence calculated at 26.5 times higher than general population estimates in one case series (Shanker et al., 2024).
    - **Thyroid Cancer:** One study of US veterans found a higher prevalence of thyroid cancer compared to non-transgender men, with a higher incidence of the more aggressive Hürthle cell cancer subtype (Christensen et al., 2024).
    - **Abnormal Sperm & DNA Damage:** The treatment results in higher proportions of sperm abnormalities, including low sperm count, poor motility, and azoospermia (absence of sperm). Analysis of testicular tissue after orchiectomy revealed that 65% of cases showed cellular atypia mimicking germ cell neoplasia (a precursor to cancer) (de Roo et al., 2025; Riva-Morales et al., 2025).
    - **Other Neoplasms**: Meningiomas and pituitary tumors (prolactinomas) identified as principal adverse drug reactions in pharmacovigilance databases (Gomez-Lumbreras & Villa-Zapata, 2024; Yelehe et al., 2022).
- **Neurological, Cognitive, and Psychiatric Harm:**
    - **Cognitive Decline**: Long-term users show significantly lower scores in information-processing speed, episodic memory, and crystallized intelligence (van Heesewijk et al., 2025).
    - **Adverse Brain Structural Changes**: Associated with decreased overall brain volume, reduced cortical thickness, and increased ventricular volume (Hulshoff Pol et al., 2006; Seiger et al., 2016; Zubiaurre-Elorza et al., 2014).
    - **Mechanistic Concerns**: Recent hypotheses suggest that estrogen acts on astrocytes, potentially altering cerebral blood flow, brain water metabolism (resulting in tissue dehydration), and metabolite concentrations (e.g., glutamate), providing a potential mechanistic link to observed structural changes and increased stroke risk (Zubiaurre-Elorza et al., 2025). Changes in the brain have also been linked to cognitive decline and dementia, as observed by van Heesewijk et al. (2025).
    - **Reduced BDNF**: Associated with reduced serum Brain-Derived Neurotrophic Factor (BDNF), a marker linked to depression risk (Fuss et al., 2015; Emon et al., 2020).

- **Reproductive Harm and Permanent Sterility:**
    - **Irreversible Infertility**: Leads to spermatogenic arrest, testicular atrophy, hyalinization, and fibrosis in a majority of cases, rendering individuals permanently sterile (Matoso et al., 2018; Cheng et al., 2019; de Roo et al., 2025).
    - Fertility preservation counseling is often inadequate or even completely absent (Bayar et al., 2023).
- **Systemic and Metabolic Harms:**
    - **Metabolic Syndrome/Diabetes Risk**: Increases fat mass and worsens insulin resistance (HOMA-IR increased 72% in the first year) (Spanos et al., 2020; Colizzi et al., 2015).
    - **Autoimmune Disease**: Associated with triggering or exacerbating conditions like multiple sclerosis (adjusted rate ratio 6.63), lupus, and systemic sclerosis (Pakpoor et al., 2016; Salgado et al., 2022).
    - **Pancreatitis:** Case studies link estrogen use to both hypertriglyceridemia-induced and gallstone pancreatitis (Chaudhry et al., 2021; Freier et al., 2021).
- **All-cause Mortality**
    - **80% increase in the standardized mortality ratio** (SMR) compared to the general population males over five decades, with cardiovascular disease a leading cause (de Blok et al., 2021). Mortality rates start to diverge significantly after age 30, reaching more than three times higher by the 50s (Hughes et al., 2022, online appendix, Table A2).
    - **Suicide:** Analysis of the United States Transgender Survey 2015 (USTS 2015) data showed that males who took cross-sex estrogen for gender affirmation were more likely to plan suicide, attempt suicide, and require hospitalization for a suicide attempt. (Biggs, M., 2022).

### B. There is a lack of substantial evidence that estrogen improves psychosocial outcomes in natal males.

The dominant public justification for the off-label use of estrogen in gender transition care is that it purportedly reduces suicidality. It is important to note, though, that this claim lacks "substantial evidence of effectiveness," the threshold necessary to support drug approval. Substantial evidence of effectiveness means evidence derived from adequate and well-controlled investigations (21 U.S.C. § 355(d); 21 C.F.R. § 201.80(e)). This standard has not been met. Long-term randomized controlled trials (RCTs) that represent the gold standard are absent. Furthermore, well-designed observational studies that follow cohorts over the medium- or long-term are also lacking. No evidence exists demonstrating that estrogen therapy decreases suicide risk in biologically male patients. The latest systematic review and meta-analysis (Miroshnychenko et al., 2025) concluded that "[t]here is considerable

uncertainty about the effects of GAHT," and that they "cannot exclude the possibility of benefit or harm," and other systematic reviews in recent years have arrived at similar conclusions (Taylor et al., 2024; Zepf et al., 2024; Ludvigsson et al., 2023; Brignardello-Petersen et al., 2022).

- **Increased risk of suicide**: A reanalysis by Biggs (2022) of survey data used by Turban et al. (2022) found that "Males who took estrogen [for gender affirmation] are more likely to plan suicide, to attempt suicide, and to require hospitalization for a suicide attempt." These findings directly undermine the claimed lifesaving benefit.

- **Failure to Demonstrate Benefit in Males:** The highest-profile prospective cohort to date—Chen et al. (2023) in the New England Journal of Medicine—was observational rather than randomized or controlled and therefore cannot establish causality. Even so, this study did not demonstrate that hormone treatment prevents suicide (***the most common adverse event after hormonal treatment was suicidal ideation,*** **and there were *two deaths by suicide that occurred within the first 12 months of the study***), nor did it include long-term follow-up sufficient to assess rare or delayed adverse outcomes. Furthermore, while reporting a clinically insignificant decrease in depression/anxiety for females on testosterone, **the study found no corresponding psychosocial improvement among the 111 natal males receiving estrogen over two years**.

- **Clinical practice not aligned with research:** The highly regarded Cochrane review in 2020 on the use of antiandrogen, estrogen, or both among transgender women (Haupt et al., 2020) found insufficient evidence of efficacy, concluding: "***This lack of studies shows a gap between current clinical practice and clinical research***."

- **Critiques of Existing Guidelines and "Consensus":** Endorsements by some U.S. medical organizations do not constitute "substantial evidence" by FDA standards. These endorsements have faced increasing criticism for lacking rigorous evidentiary support and resting on a "consensus" that is not evidence-based. The independent Cass Review (2024), commissioned by England's NHS, found the evidence base for pediatric gender interventions to be "remarkably weak."

  This critique of poor quality and circularity is substantiated by a systematic review conducted between April and December 2022 of 23 international guidelines by Taylor et al. (2024), which found that the developmental rigor of major U.S. guidelines was exceptionally low: the American Academy of Pediatrics (AAP) 2018 guideline scored 12% for rigor, and the American Psychological Association (APA) 2015 guideline scored 24%. The review concluded that these guidelines lack an independent, evidence-based approach and, as a result, the reviewers unanimously recommended *against* their use in practice.

  Furthermore, the review also highlighted the "interrelated nature" of the guidelines: most of the clinical guidelines cite one another in a circular manner, relying on each other's

conclusions to legitimize their own. This circularity arose because two foundational documents—the Endocrine Society's 2009 guidelines and WPATH 7—influenced nearly all subsequent guidelines. These two original guides were already closely interlinked, with WPATH adopting Endocrine Society recommendations while also co-sponsoring and providing input on its drafts. This created a feedback loop: the current WPATH 8 guidelines, for example, cite other national guidelines as support, even though those guidelines were themselves heavily influenced by the previous WPATH 7 guidelines. This pattern of self-referencing has created a false appearance of consensus based on circularity rather than high-quality evidence.

This practice of self-reinforcing citation, rather than a foundation of rigorous, unbiased evidence, is ethically indefensible when patient welfare is at stake. This finding aligns with recent policy shifts in several countries that pioneered these medical interventions, such as Sweden, Finland, and Norway, but have now restricted them. This international divergence and methodological failure underscore the profound scientific uncertainty about these interventions.

- **Specific Concerns for Vulnerable Populations:** A retrospective chart review at a U.S. pediatric gender clinic in 2016 found that 23% (9/39) of patients aged 8–20 screened *possible, likely,* or *very likely* for Asperger syndrome on the Asperger Syndrome Diagnostic Scale (ASDS) (Shumer et al., 2026). This finding of 23% prevalence in 2016 is more than seven times higher than the current prevalence in the general youth population (3.2%), a rate the Department of Health and Human Services (HHS) has recently termed a 'rampant epidemic'. Among those screening high, the cognitive and maladaptive subscales were most elevated, and many had additional psychiatric diagnoses. The authors emphasized that the ASDS is a screening tool, not diagnostic, and recommended routine autism assessment for all gender-dysphoric youth.

  This **over seven-fold overrepresentation of autism spectrum traits** exposes a critical diagnostic vulnerability: how to distinguish autism-related characteristics—such as cognitive rigidity, restricted or obsessional interests, sensory sensitivities, and social-communication deficits—from a persistent, identity-based gender dysphoria. A 2016 narrative review, co-authored by Dr. Annelou de Vries, architect of the "Dutch Protocol," reached the same conclusion: "no conclusions could be drawn about the optimal diagnostic procedure, treatment protocol, and treatment outcomes in gender dysphoric individuals with co-occurring ASD." (Van Der Miesen, Hurley, & De Vries, 2016).

  Despite this longstanding uncertainty, irreversible hormonal interventions continue to be prescribed to a population in which social cognition, abstract reasoning, and risk appraisal may be compromised. In regulatory terms, this represents a clear failure of informed consent and risk mitigation.

- **Failure of the "Affirmation" Model:** The current "affirmation" model, under which estrogen is recommended for natal males, lacks necessary safeguards. To prevent "box-checking," a rigorous diagnostic process is required. The Finnish model (Kaltiala, 2025) provides a template, mandating exploratory psychotherapy as the first-line

treatment and requiring co-morbid psychiatric conditions to be well-controlled *before* any medical referral. This process, which often takes over a year and involves multiple meetings with the young person and their parents, stands in stark contrast to the rapid "affirmation" model in the United States and represents a true, non-circumventable safeguard against any overzealous medicalization. (Of note, the recent peer-reviewed report from the HHS on pediatric gender dysphoria also identifies this course of action as the evidence-based best practice.)

- **Presence of Other Co-morbidities:** High rates of trauma, depression, anxiety, and personality-disorder traits further complicate the clinical picture and raise urgent questions about whether hormonal interventions address the root causes of distress or leave them unmitigated.

  A recent nationwide registry study from Finland (Ruuska et al., 2024) examined all-cause and suicide mortality among gender-referred adolescents and young adults. Although the cohort showed an elevated suicide rate, the absolute number of suicides was rare, and—crucially—the risk became statistically non-significant after adjusting for the participants' extensive psychiatric treatment histories. The authors concluded that **underlying psychiatric morbidity, not the gender dysphoria diagnosis itself, was the primary predictor of suicide mortality and that medical gender reassignment did not alter suicide risk.**

  This evidence strongly suggests the root cause of distress and suicide risk is the underlying psychiatric co-morbidity, which hormonal interventions do not resolve.

  These data underscore a critical public-health imperative: effective suicide prevention for gender-distressed youth must begin with early identification and treatment of underlying psychiatric illness. Addressing trauma, depression, and other co-morbidities through comprehensive mental-health care is the most evidence-supported path to reducing suicide risk in this population.

### C. Estrogen is commonly prescribed for feminization of natal males—a condition for which it is not approved.

The administration of systemic estrogen, often in conjunction with anti-androgens, to induce feminizing changes in natal males has gone from being a relatively uncommon practice to a widespread, standard component of "gender-affirming care" protocols in the United States, despite lacking FDA approval for this indication. *The commonality of this practice* is substantiated by multiple lines of evidence:

- **Endorsement in Clinical Guidelines:** Professional organizations—including the Endocrine Society, the World Professional Association for Transgender Health (WPATH), the American Medical Association (AMA), the American Psychiatric Association (APA), and the American Academy of Pediatrics (AAP)—currently endorse this off-label use of cross-sex hormones for the treatment of gender dysphoria. However, "agreement among organized medicine leaders alone does not constitute evidence" (Makary, M. (2024).

*Blind Spots: When Medicine Gets It Wrong, and What It Means for Our Health* (1st ed.). Bloomsbury Publishing USA).

In the last couple of years, these endorsements have faced increasing criticism for lacking rigorous evidentiary support and resting on a "consensus" that is not evidence-based (see Section B, "Critiques of Existing Guidelines and 'Consensus'," for details on how this "consensus" was artificially manufactured). Nevertheless, their guidelines and policy statements have become de facto national and international protocols, shaping what many clinicians describe as the "standard of care." In recent times, several countries, including England, Sweden, Finland, and Denmark, among others, have increasingly distanced themselves from that consensus. More importantly, these guidelines do not constitute FDA-recognized standards of evidence or safety, and they rely heavily on the subjective selection of uncontrolled, short-term observational studies.

- **Proliferation of Specialized Clinics:** The number of clinics providing hormonal interventions for gender affirmation based solely on informed consent has surged. A 2022 Reuters investigation documented the growth of specialized pediatric gender clinics from zero to over 100 in just 15 years, while a 2021 analysis estimated that there were more than 300 clinics and offices providing such interventions to minors nationally (Reuters, 2022; SEGM, 2021). In addition to these clinics, nearly 450 centers of Planned Parenthood now offer gender transition hormones for young adults, according to insurance claims data (The Free Press 2024). The scale of this issue is amplified by the growing number of online clinics serving only this demographic, such as FOLX Health, Plume, True U Clinic, Howard Brown, GenderGP, and QueerDoc. "Informed consent" models typically prescribe anti-androgens and cross-sex hormones based on patient self-identification, often with limited assessment of underlying medical or psychiatric conditions. Critics argue that this approach risks overlooking co-morbidities and may contribute to the increasing number of individuals reporting regret or detransition, as documented by advocacy and research organizations including the Society for Evidence-Based Gender Medicine (SEGM), Genspect, and the LGB Courage Coalition.

- **Significant Patient Numbers:** Recent data indicate substantial uptake. A 2025 study in *JAMA Pediatrics* estimated that approximately 1 in 1,000 adolescents received cross-sex hormones under private insurance by the time they turned 17 (Hughes et al., 2025). This demonstrates the large scale of these interventions within just one demographic segment.

  Even so, this 1 in 1000 rate is likely a **significant undercount**. The methodology of the Hughes et al. (2025) study relied on identifying prescriptions linked *only* to formal diagnoses of gender dysphoria (F64.x and Z87.890). It necessarily excludes widespread prescribing that occurs under less specific diagnostic codes, such as 'Endocrine Disorder, Unspecified' (ICD-10 E34.9, ICD-9 259.9), a practice used by clinicians to navigate insurance reimbursement. Indeed, a recent chart review study found that the

code E34.9 was used in nearly as many gender-diverse patients as the specific gender dysphoria codes (Hines et al., 2023). Therefore, the true prevalence of this off-label use is almost certainly far greater than what is captured by these already alarming data.

- **Diagnostic Inflation and Treatment of Non-Clinical Populations**: Current prescribing practices appear to be capturing a population that is clinically distinct from the cohorts studied in historical literature. A recent methodological commentary analyzed the prevalence of gender-affirming hormone use in US adolescents (based on the Hughes et al. 2025 data). They found that the current rate of medicalization based on formal diagnoses of gender dysphoria (0.1%) is 13 to 22 times higher than the established historical clinical baseline for gender dysphoria (0.0046%–0.0075%). The authors conclude that this discrepancy suggests a "systematic over-prescription of medical interventions to an overwhelmingly non-clinical population." This implies that the overwhelming majority of adolescents currently receiving off-label estrogen likely would not have met the diagnostic criteria used in the foundational studies (e.g., the Dutch Protocol), rendering the existing (and already weak) evidence base inapplicable to the current patient population. (Schwartz & Lal, 2025).

- **Extensive Body of Literature:** The breadth of published research on gender-affirming hormone therapy (GAHT) reflects the widespread and entrenched nature of the practice. Proponents cite more than 2,000 studies published since 1975 (Endocrine Society Newsroom, 2023) to suggest an established evidence base. *Yet, the sheer volume of publications primarily documents routine clinical use, rather than a rigorous demonstration of benefit, particularly for psychosocial outcomes*.

  Concerningly, a substantial portion of this literature now reports serious and persistent adverse outcomes. A recent compilation of safety signals associated with estrogen by Schwartz et al. (2025) identified dozens of studies that describe medical, psychiatric, and psychosocial harms associated with hormonal transition interventions (Schwartz et al. 2025). The growing number of outcome studies highlights both the scale of off-label prescribing and the lack of definitive, well-controlled trials that establish whether the benefits of off-label prescribing outweigh the risks.

### D. Regulatory Precedent: The Case of DES (Diethylstilbestrol)

In 1941, Diethylstilbestrol (DES), a synthetic estrogen, was approved by the FDA for specific gynecologic indications (FDA, 2023). However, physicians began prescribing it off-label for a range of conditions, notably the prevention of miscarriage. Despite a limited number of toxicology investigations and emerging animal studies in the late 1930s and 1940s (European Environment Agency, 2001) that revealed carcinogenic potential, the FDA approved a supplemental indication for miscarriage prevention in 1947 (Herbst, 2015).

Between 1938 and 1971, millions of women were exposed to DES (Institute of Medicine (US) Committee on Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies,

1994). Crucially, by 1953, a landmark double-blind study (Dieckmann et al., 1953) demonstrated that DES offered **no measurable benefit** in preventing miscarriage. Yet, the medical establishment continued to use it widely for another two decades (Giusti et al., 1995).

Just as early DES harm signals were overlooked, current signals of harm, including thrombosis, stroke, cancer, and other risks of estrogen prescribed to natal males (Schwartz et al., 2025), are not being addressed. Prescription of estrogen for natal males has continued despite failure of studies to show evidence of benefit on psychosocial outcomes, while evidence of harm accumulates. "The best available evidence reporting on the effects of GAHT in individuals with GD ranged from moderate to high certainty for cardiovascular events and low to very low certainty for the outcomes of GD [gender dysphoria], global function, depression, sexual dysfunction, BMD [bone mineral density], and death by suicide" (Miroshnychenko et al., 2025).

The long-term reproductive consequences of Diethylstilbestrol (DES) use were not fully evident until 1971 (European Environment Agency, 2001), when the first evidence was published. This key finding linked prenatal exposure to DES with the development of clear cell adenocarcinoma of the vagina and cervix in young women, marking the beginning of understanding its long-term toxicity. Seven months after this initial publication, the FDA withdrew approval for the use in pregnant women (Western Journal of Medicine, Calif Med, 1972) to prevent miscarriage (European Environment Agency, 2001, Jishi and Sergi, 2017).

Relying on short-term observational studies to justify the lifelong off-label use of estrogen in natal males risks repeating this historic error. Substantial harm signals, as previously discussed, demonstrate that estrogen therapy in natal males can cause life-altering and life-threatening adverse effects. However, in the absence of a dedicated registry or mandatory, rigorous adverse-event reporting, the true incidence and prevalence of these harms in this population remain unknown.

The FDA's response to the DES crisis provides a roadmap for today. In its November 1971 Drug Bulletin regarding DES (FDA Drug Bulletin, November 1971), the FDA acknowledged that the data showed 'only an association and not necessarily a cause-and-effect relationship,' yet, the agency did not use uncertainty as an excuse for inaction. We urge the FDA of today to follow this precautionary standard in the face of such accumulating evidence of harm.

### E. Conclusion: Urgent Need for FDA Action

The confluence of widespread common use, a profound lack of evidence of effectiveness, particularly as it relates to psychosocial outcomes (especially in vulnerable subgroups), and a substantial and growing body of evidence detailing severe, life-altering, and potentially fatal harms creates an urgent public health imperative. The current labeling for estrogen-containing products fails to adequately warn clinicians and patients about the specific dangers inherent in this off-label application, which undermines the principles of

informed consent and patient safety.

In alignment with the Secretary of the U.S. Department of Health and Human Services' commitment to a radical transparency agenda, this petition requests the elimination of a significant gap in regulatory oversight. The criteria under 21 C.F.R. § 201.80(e) are clearly met. We therefore urge the FDA to initiate the requested actions: open a dedicated docket, convene a Part 15 public hearing, and subsequently implement recommended regulatory measures, including a boxed warning and guidance for medical providers, to address this critical issue.

## III. ENVIRONMENTAL IMPACT

The actions requested in this petition are either procedural (opening a docket and holding a hearing) or related to drug labeling and safety communications. These actions will not significantly affect the quality of the human environment and are categorically excluded under 21 C.F.R. § 25.30.

## IV. ECONOMIC IMPACT

Information on the economic impact will be submitted upon request by the Commissioner.

## V. CERTIFICATION

The undersigned certify that, to the best of their knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners that are unfavorable to the petition.

Respectfully submitted,

**Lauren H. Schwartz, MD**
(b) (6)
[redacted]

**Filed on behalf of Petitioners:**

Organizations:
Partners for Ethical Care - PartnersForEthicalCare.com
Our Duty USA - OurDutyUSA.org
LGB Courage Coalition - LGBCourageCoaltion.org
The Center for Bioethics and Culture - CBC-Network.org

Colorado Principled Physicians - ColoradoDoctors.org
Genspect International - Genspect.org
Genspect USA - Genspect.org
PITT Parents - PITTparents.com
Texas Principled Physicians - TexasDocs.org
Parents of Desisters - ParentsofDesisters.info
Family Institute of Connecticut Action - CtFamily.org
American College of Pediatricians - ACPeds.org
Democrats for an Informed Approach to Gender - Di-AG.org
Women's Liberation Front - womensliberationfront.org
Do No Harm - donoharmmedicine.org

Medical or Psychological Professional and/or Researcher:

Patrick Lappert, MD
Miriam Grossman, MD
Evelyn Ball, LMFT
January Littlejohn, LMHC
Dr. Javier Perez
Katherine Locke, RN
Dr. Chad
Lori Addesa, RN
Alice Rose-McDonald, RN
Brenda Smith, RT
Lauren Schwartz, MD, DFAPA, DABPN
Susan Green, RN
Dr. Greg Carter
Dr. Patrice N. Stevenson
Maria Arana, NP
Sharon Barnes, COTA/L
Frank M Tursi, DO
Sandy Casciato, CRNA
Evelyn Duvivier, MD MPH
Dr. Joanne Sinai
J. Cohn, PhD
Patrick Hunter, MD MSc
Dr. Gus Toma
Whitney Jones, MD
Victoria Hall, MSN, FNP-C
David Boettger MD, MS, FAAP
Eithan Haim, MD
Jennifer Lahl, MA, BSN. RN
Dr. Justin McCoy
Greg Merrell, MD
Mark Hickman, MD
W. Anthony Gerard, MD
Kristine M. Rivera, DO
Liza Saplala Stanton, MD
Matthew Clark Poling, MD
Richard H. Sandler, MD
Andre Van Mol, MD
Laura J. Haygood, MD
Kathleen Goonan, MD
Tim Millea, MD
Travis J. Morrell, MD, MPH
Marcia Schor
Kimberly A. Vacca, MD
Tara Simone Williams, MD
A.Singhal, MD
Arthur J de Lorimier, MD
Molly Plautz, RN
Jessica Dawson, LMHC
Kinloch Nelson, MD
Michelle Cretalla, MD
Alfonso Oliva, MD, FACS
Lisa Ehrlich, MD, FACP
Stephen Doane, MD
Jennifer Petrillo, MD
Callie Dagen, MD
Katherine Welch, MD
Jill Butler, MD FACP
Daniel Weiss, MD
Jared L. Ross, DO
Lauren Phillips, PA-C

D. Michael Ready, MD
Carrie D. Mendoza, MD, Emergency Medicine, State of Illinois Lt. Governor Candidate 2026
Roy Eappen, MDCM FACP FRCP(c) FACE CD
Melanie Crites-Bachert, DO FACOS FACS
Kathy Platoni, Psy.D, DAAPM, FAIS, COL (RET.)

Public Health/Government/Policy Expert:
Peter J. Pitts, Former FDA Associate Commissioner
Lauren Wohl-Sanchez
Dedra Jones
Jean Parker, Bioethics Professor

Legal Professional:
Victoria Albanesi
Tena Zara
Linda Kristina Palumbo
Phillip Stanton
Kathleen H. Dooley
Nancy Stade

Academic/Educator:
Rebecca van Kniest
Karole Fedrick
Nicole Kaucher

Impacted Patient:
Forrest Smith
Billie Burleigh
Rene Jax
Cori Cohn
Jeff Tooley

Concerned Parent or Family Member:
K. Mulligan
Melody Glazer
Susan Zamecnik
Amanda Quick
Sheila Scheve
Stephanie G
SS
Patricia Riefenstein
John Petersen
Shyam Krishnamurthy
Joanna Kingsbury
Julianne Verhagen
Cathy Hoover Groen
Gregory Araya
Erin Sardiello
Christine Chang
EA Dolan
Stephanie M
Ragnhild
Laurie E. Samuelson

Rebecca K.
Rosanna Rodriguez
Lisa Shultz
K. Quigley
Ann Von Lehmen
Debbie Popovchak-Erickson
Christy Emory
Angela Molin
Camela Bryan
Tom Quigley
Monique vT
A Carnes
Brain Tumor Brandon
Kathleen Chitwood
Charlotte Johnson
Julie Framingham
Beth Bourne
Christine Goff
Jessica Ludeke
Laureen Boll
Stephanie Barnes
Gary Barnes
D. Singhal
Joanne Smart
John Furton
Lynnanne Knippel
Sarah A.
Juliann Zoetmulder
David Atkinson
Laci Olson
Mary Stout
BJ Jackson
Ruth Johnston
Catherine Henderson
Cynthia MacAdam
David Johnston
Leslie Miller
Diana Terlato
Scott MacAdam
Natalie Wheeler
Lost Boy Mom
Summer Yule
Katie Guy

Hayley Meagan
L Forte
Victor Esterlit
Windy Horton
Fiona Miller
Kim Johnson
Cally Furton
Mae Lyle
Stephanie Peecher
Doug Throckmorton
Suzanne Counsel
Parent of male taking estrogen
Concerned Parent
Jaclyn Gouge
Erin Sardiello
Katherine Winslow-Duehr
Gary Duehr
Miles Winslow
David Smith
Roberta S.
Erin Darlington
Denise Menagh
Vicki Wooledge
Dale Hoard
Lisa E.
Christin Manning
Nonna S.
Violet Dunai-Orlesky
DP
Melanie Erdmann
Amy M. Scott
Susan Lee Cary
Mark Stewart
Garth Hill
PM Bailey
Kelly Wehrer
A. Hariri
Carolynn Christenson
William Palaia
Amy Raf
Mark Christenson

Nicole Sorem

Kristin Jackowick

Concerned Citizen:

Teresa Winship
Roland Samuelson
Vasanth Krishnamurthy
Ben Davis
Marlene Suzuki
Sven Scharpen
Dedra Jones
Hayley Steen
Bob Renate
Emma Stewart
Tami Blayney
Jennifer Patt
Catherine Bowen
Cari Roundy
Ken Rankin
Michelle DeAlmeida
Karen Riordan
Mary Stout
Stacey Layne
T. Debolt
David Ness
Brook Hines
Brenda Ragosta
Vincent Ragosta
Sam Adam
Sue D.
Connie Hahn
Richard C. Guggenheim
Cecelia Wu
Laura Becker
Jennifer Stanley
Maureen Killoran
Melissa Brown
Theresa Orlando
Eileen Christian
Donna Squires
Ruby M.
James Brown
Aida Cerundolo