CITIZEN PETITION

The undersigned individuals—Jay T. Allen, MD, Miriam Grossman, MD, Patrick Hunter, MD, William Malone, MD, Quentin van Meter, MD—and organizations—Detrans Help, Foundation Against Intolerance and Racism (FAIR) in Medicine, Gender Dysphoria Alliance, Gender Exploratory Therapy Alliance, Genspect, International Partners for Ethical Care, Our Duty USA, and Rethink Identity Medicine Ethics—submit this petition under 21 C.F.R. § 10.30 to request the Commissioner of Food and Drugs to take urgent action concerning the off-label use of GnRH agonists, a class of drugs also known as puberty blockers.

Petitioners are a coalition of physicians and organizations of parents, professionals in the healthcare field, individuals who have transitioned, and detransitioners dedicated to improving care for minors. We are concerned by the dramatic increase in the off-label use of puberty blockers to treat children with gender dysphoria, a diagnosable condition in the Diagnostic and Statistical Manual of Mental Disorders 5,¹ that entails deep distress over one’s biological sex. Despite the widespread—and rapidly growing—use of these drugs in this population, and despite serious known and potential risks from these drugs, this use has never been evaluated for safety and effectiveness by the FDA.

Although this use has not been approved by the FDA, the FDA must not turn its back on the potential harm to children from continued use of a drug with known risks and unproven benefits. We are asking the FDA to fulfill its public health mission by commissioning a comprehensive analysis of existing studies concerning this use, by seeking new, long-term studies of this use, by promoting awareness of the state of evidence concerning this use and that this use is off-label, and by alerting manufacturers and health care providers that because this use is unapproved, it is unlawful to promote this use—directly or indirectly. These actions are needed to understand the long-term risks and outcomes associated with the use of puberty blockers in children with gender dysphoria, to promote public awareness that this use has not been shown to be safe or effective, and to prevent further harm to this vulnerable population.
**Actions Requested**

1. Commission a systematic review of this off-label use by the National Academy of Sciences, Engineering, and Medicine (NASEM).
2. Issue written requests under the Best Pharmaceuticals for Children Act (BPCA) for long-term registry studies of this off-label use.
3. Create a dedicated web page concerning this off-label use.
4. Alert manufacturers and providers to the consequences of unlawful promotions of this off-label use.

**Statement of Grounds**

I. The Off-Label Use of Puberty Blockers in Children is Increasing.

In recent years, there has been a dramatic rise in the number of children who seek clinical treatment for gender dysphoria. Reuters recently published an analysis finding that, in children ages six to seventeen, diagnoses of gender dysphoria have nearly tripled between 2017 and 2021. These recent increases follow a steady rise in referrals to gender clinics over the past two decades.

In the United States, children who seek treatment for gender dysphoria are likely to be treated according to what is known as the affirmative model, so called because the goal of treatment is to affirm the child’s self-reported gender-related distress without providing a complete differential diagnosis. This is so despite evidence that children with gender dysphoria have higher rates of other psychological and developmental conditions, including autism, eating disorders, and depression. For these children, puberty blockers are often the first in a series of medical interventions prescribed as part of the affirmative model; medical interventions under this model commonly progress to cross-sex hormones (estrogen for males and testosterone for females) and may progress to surgeries to cosmetically align with the opposite sex (such as double mastectomy for females, facial feminization for males, and genital surgeries with high rates of complication, such as vaginoplasty and phalloplasty). Because of the prevalence of the affirmative model in the United States, the number of children with gender dysphoria receiving puberty blockers has also risen sharply, more than doubling between 2017 and 2021.

Puberty blockers, or gonadotropin-releasing hormone (GnRH) agonists, are a class of drugs that are FDA-approved for treating certain cancers, endometriosis, and, in pediatric populations, central precocious puberty. These drugs suppress the release of sex-specific hormones—testosterone in males and estrogen in females. When given to children in the early stages of puberty, they delay sex-related changes normal to adolescent development, such as deepening voice in males and breast development in females.

The affirmative care model rests on the assumption that these changes are uniquely distressing to children with gender dysphoria. In the early 1990’s, doctors in a Dutch clinic pioneered the use of GnRH agonists to block these changes from occurring in young adolescents experiencing distress about their gender. This use of puberty blockers was exceptional; over time, however, this use became part of a standard treatment protocol. The original “Dutch protocol” included guardrails intended to limit the treatment to children most likely to benefit, such as limiting the protocol to children aged 12 and over. Today, many of these guardrails are ignored. Standards of care recommend puberty blockers to children as young as nine years old to prevent the onset of puberty.
Brand name puberty blockers include Lupron Depot-PED, Supprelin LA, Fensolvi, Synarel, and Triptodur. The FDA recently required new safety information in the labeling for these drugs after multiple incidents of idiopathic intracranial hypertension in children taking them. This update followed a 2016 mandatory safety update to reflect the risk of new or worsened psychiatric problems, including depression and suicidal thoughts, in children taking the drugs. The labeling of Lupron Depot-PED includes the following in its discussion of post-market experience with the drug:

**Psychiatric Disorders:** Emotional lability, such as crying, irritability, impatience, anger, and aggression has been observed with GnRH agonists, including LUPRON DEPOT-PED [see Warnings and Precautions (5.2)]; Depression, including rare reports of suicidal ideation and attempt, has been reported for GnRH agonists, including LUPRON DEPOT-PED, in children treated for central precocious puberty. Many, but not all, of these patients had a history of psychiatric illness or other comorbidities with an increased risk of depression.

These are just some of the risks that the FDA requires manufacturers to describe in the labeling for puberty blockers. Yet puberty blockers have been marketed directly to teenagers with promotions that characterize the drugs as a safe way to “put puberty on hold,” without disclosing any of the required risk information.9

II. The Benefit-Risk Profile of Puberty Blockers in Children with Gender Dysphoria is Unknown.

When given to children, puberty blockers may pose many additional risks that have not been adequately studied. What is most concerning is that, because puberty blockers are not FDA-approved in children with gender dysphoria, there is no demonstrated benefit of the drugs to justify these risks. This is why Sweden, Finland, the UK, Norway, and other countries have all turned against the use of puberty blockers and other medical interventions as a front-line treatment of gender dysphoria, recognizing this use as experimental.

A. Puberty blockers pose risks to bone health, fertility, and neurocognitive development.

There are several known and potential risks of puberty blockers, some of which appear on the FDA approved label and some of which do not. The label of Lupron Depot-Ped describes multiple warnings, precautions, and adverse events in addition to the risks discussed above of idiopathic intracranial hypertension and “psychiatric events.” The label also warns of the potential for convulsions and an initial increase in “clinical signs and symptoms of puberty, including vaginal bleeding.” In other words, the drugs initially cause the onset of symptoms they are intended to block.10

Main stream publications are increasingly sounding the alarm about other established risks of these drugs that do not appear as adverse effects in the FDA approved label, such as the effect of puberty blockers on bone mineral density.11 It is well-known that puberty blockers interfere with bone development, raising concerns about osteoporosis and fracture. Bone density surges in untreated teens, but teenagers do not gain bone density while taking the drugs.12 Proponents of the use of puberty blockers in children with gender dysphoria claim any effects on bone density are fully reversible when children stop taking the drugs, an optimism parroted in the approved label of Lupron Depot-Ped, which states:
Published literature and postmarketing reports indicate that bone mineral density may decrease during GnRH therapy in pediatric patients with central precocious puberty. Published studies indicate that after discontinuation of therapy, subsequent bone mass accrual is preserved and peak bone mass in late adolescence does not seem to be affected.\textsuperscript{13}

In fact, whether bone development catches up in children exposed to these drugs has not been established, but some studies suggest that the opposite is true—that is, that these children continue to show deficits in bone density after they discontinue puberty blockers.\textsuperscript{14}

An additional adverse effect that is well-established is infertility. Studies have found that large majorities of children with gender dysphoria given puberty blockers go on to take cross-sex hormones,\textsuperscript{15} and blocking puberty (with GnRH agonists) then promoting changes associated with the puberty experienced by the opposite sex (with cross-sex hormones) prevents the natural course of a child’s puberty from ever occurring. The risk of infertility is so well established that standards of care recommend that practitioners discuss this risk and “fertility preservation options” before beginning treatment.\textsuperscript{16} Yet, pharmaceutical companies are under no obligation to warn users of this serious side effect of their drug because it is a consequence of the off-label use of puberty blockers followed by the off-label use of cross-sex hormones. The consequence of this course of treatment is irreversible infertility, an outcome children and adolescents may not fully understand when providing consent to treatment.

Similarly, the label of puberty blockers fails to disclose effects of the drugs on neurocognitive development because such effects have not been adequately studied. The adolescent brain undergoes changes rivaled only by those that occur in neonatal development,\textsuperscript{17} yet the neurocognitive effects of “pausing” puberty in adolescents is poorly understood. A group of experts in adolescent development—including prominent advocates of the affirmative model—developed consensus around the need for further study of the neurodevelopmental effects of puberty blockers, noting that “pubertal suppression may prevent key aspects of development during a sensitive period of brain organization.”\textsuperscript{18}

In sum, these drugs are known to interfere with bone development and fertility (when followed by cross-sex hormones) and serious concerns exist about their effect on long-term bone health and neurocognitive development. What is most concerning is that this safety profile is currently tolerated in drugs prescribed to children for which the benefit is highly uncertain.

**B. The benefit of puberty blockers in children with gender dysphoria has not been shown.**

The evidentiary basis for using puberty blockers in children with gender dysphoria is increasingly under attack. Two longitudinal studies are commonly cited as vindication for current, permissive treatment approaches to giving puberty blockers under the affirmative care model. It is fair to say these studies form the foundation for the use of puberty blockers in gender distressed youth; the Society for Evidence-Based Gender Medicine notes:

> [c]ritics and proponents of youth gender transition agree that to date, the Dutch studies represent the best available evidence for pediatric gender transition, and indeed the entire model of “gender-affirming” care is based on the Dutch experience. The seminal importance of the Dutch studies is evidenced by the fact that the Endocrine Society Guidelines, and WPATH “Standards of Care 7” under which the practice proliferated, refer only to the Dutch experience as proof of “benefits” of the practice.\textsuperscript{19}
These studies followed a cohort of seventy adolescents treated with puberty blockers. At ages 14-19, following administration of puberty blockers, the study authors reported that: “[b]ehavioral and emotional problems and depressive symptoms decreased, while general functioning improved.”20 At ages 19-22, within a year of “gender reassignment” surgery, the second study reported that “gender dysphoria had resolved, psychological functioning had steadily improved, and well-being was comparable to same-age peers.”21

These studies have come under sharp criticism in recent scientific reviews. For example, one review notes the small sample size, compounded by significant attrition so outcome measures were available for subsets of patients numbering only between 32 and 55.22 Patients lost to follow up included eight who simply refused to participate further, in addition to:

one patient killed by necrotizing fasciitis during vaginoplasty. The authors did not mention fact that this death was a consequence of puberty suppression: the patient’s penis, prevented from developing normally, was too small for the regular vaginoplasty and so surgery was attempted with a portion of the intestine, which became infected.23

This review further notes that the follow-up period was too short for treatments that may entail irreversible change and lifelong medication. Another review published in 2023 characterized the studies as “methodologically flawed,” concluding they “should have never been used in medical settings as justification to scale this ‘innovative clinical practice.'”24

More recent studies have not closed this evidentiary gap. The critiques of the Dutch studies are echoed in recent comprehensive scientific reviews by national health authorities that have also covered subsequent studies of puberty blockers. In 2020, the United Kingdom’s National Health Service (NHS) commissioned a review “to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gonadotrophin releasing hormone (GnRH) analogues for children and adolescents aged 18 years or under with gender dysphoria.”25 The conclusion of the review was that:

The results of the studies that reported impact on the critical outcomes of gender dysphoria and mental health (depression, anger and anxiety), and the important outcomes of body image and psychosocial impact (global and psychosocial functioning), in children and adolescents with gender dysphoria are of very low certainty [ ]. They suggest little change with GnRH analogues from baseline to follow-up.26

A recent review of twenty-four studies conducted by the Swedish Health Authority made similar findings. That review concluded that existing evidence is “insufficient” to evaluate the effect on psychosocial and mental health.27

In short, systematic reviews have found the scientific foundation for the use of puberty blockers in children with gender dysphoria to be weak. But instead of instigating a robust scientific debate, critiques of the affirmative care model often provoke unfounded assertions about the dire consequence of withholding care. A claim that is often repeated is that children with gender dysphoria are at high risk of suicide without so-called affirmative care beginning with these drugs. The genesis of this claim may be a 2014 report of a survey of this population, in which 41% of respondents reported having attempted suicide.28 While this number is concerning, the study authors themselves noted that the methodology of
the study limited the reliability of the data, and subsequent reviews of the literature have found that “[t]here is a need for continued research in suicidality outcomes following gender-affirming treatment that adequately controls for the presence of psychiatric comorbidity and treatment, substance use, and other suicide risk-enhancing and reducing factors.” More disturbingly, a 30-year longitudinal study of over three hundred Swedish people who underwent “gender reassignment” surgery found that:

> [p]ersons with transsexualism, after sex reassignment, have considerably higher risks for mortality, suicidal behaviour, and psychiatric morbidity than the general population. Our findings suggest that sex reassignment, although alleviating gender dysphoria, may not suffice as treatment for transsexualism, and should inspire improved psychiatric and somatic care after sex reassignment for this patient group.

A recent retrospective study of adolescents with gender dysphoria similarly found “mental healthcare did not significantly change” among subjects receiving care under the gender affirming model.

These studies showing no improvement in mental health following “gender affirming” care do not focus on puberty blockers, but the findings are nonetheless relevant. Coupled with studies that show that children who pursue gender affirming care commonly have underlying mental disorders, and studies finding high rates of persistence and progression to additional treatment in children given puberty blockers, the finding that medical gender affirmation does not relieve—and may worsen—suicidality undercuts a central argument for this use of puberty blockers: namely, that withholding the drugs may provoke gender distressed youth to end their lives. Taken together, these studies suggest a different hypothesis: that puberty blockers induct emotionally troubled children into a process that may consign them to lifelong medicalization—including the potential for experimental surgeries with high rates of complication—at an age where they are too young to understand the consequences, and that this process at best ignores underlying psychological causes of distress and at worse, may deepen them.

C. There is a growing international consensus against the use of puberty blockers in children with gender dysphoria.

Proponents of the use of puberty blockers in children with gender dysphoria sometimes counter the serious health risks and lack of established benefit by noting that major medical organizations in the United States currently support this use as part of the affirmative care model. For example, the American Medical Association, the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists all support an Endocrine Society resolution to protect access to the model. But recently, twenty-one clinicians and researchers from nine different countries took the extraordinary step of publishing an open letter in the Wall Street Journal criticizing the evidence underlying these organizations’ support, stating that:

> Every systematic review of evidence to date, including one published in the Journal of the Endocrine Society, has found the evidence for mental-health benefits of hormonal interventions for minors to be of low or very low certainty. By contrast, the risks are significant and include sterility, lifelong dependence on medication and the anguish of regret. For this reason, more and more European countries and international professional organizations now recommend psychotherapy rather than hormones and surgeries as the first line of treatment for gender-dysphoric youth.
The claim that gender transition reduces suicides is contradicted by every systematic review, including the review published by the Endocrine Society, which states, “We could not draw any conclusions about death by suicide.” There is no reliable evidence to suggest that hormonal transition is an effective suicide-prevention measure.

The politicization of transgender healthcare in the U.S. is unfortunate. The way to combat it is for medical societies to align their recommendations with the best available evidence—rather than exaggerating the benefits and minimizing the risks.

But it is not only practitioners in other countries who question the affirmative model. Medical organizations’ statements of support have been issued over increasingly vigorous dissent by members. In fact, medical opinion in the United States is fractured concerning the use of puberty blockers in children with gender dysphoria and other aspects of the affirmative model, and even prominent practitioners of affirmative gender care have joined the call for greater scrutiny of the model as practiced in the United States.

With the medical community fractured, many states have acted to remove the care of these children from doctors and to place it in the political realm. While Minnesota and California have enacted laws to “provide sanctuary” for children seeking gender affirming care, including puberty blockers, multiple states have banned or restricted minors from receiving such care. Media reporting on the wave of state-level legislation limiting access to puberty blockers often refers to these measures as “anti-trans” or “anti-LGBTQ”; some reporting refers to the measures as “red state bans.” But these restrictions mirror the actions of multiple liberal democracies with advanced health care systems that have pioneered models of care for gender dysphoric youth only to reverse course in the face of mounting concerns. Countries that have curtailed youth access to puberty blockers include the United Kingdom, Sweden, Finland, Norway, and France. Given the concerns about the safety of these drugs, and the growing international consensus that evidence to support their use is lacking, the refusal of federal health officials in the United States to take a critical look at the evidentiary support for the affirmative care model is making this country an outlier among its peer nations.

III. The FDA Must Act to Protect Children from Harm.

In sum, the known and potential harms from puberty blockers are varied and serious, but the benefits are unknown. Supportive statements of major medical organizations concerning the off-label use of puberty blockers as part of the affirmative care model mask impassioned dissent in the medical community. Concerns about the lack of scientific support for medical interventions in children—and the appearance that the medical community cannot police itself—has fueled a wave of state-level restrictions, meaning that the care a child receives may be determined not by the scientific process, but by the political climate of the child’s state. We ask the FDA to exercise its mandate to ensure the safety and effectiveness of drugs and return to the realm of science the question of whether unproven pharmaceutical interventions should be given to gender-distressed kids. We ask the FDA to take the following actions to protect this especially vulnerable group of children:

1. **Commission a systematic review by NASEM of existing peer-reviewed studies on the use of puberty blockers in children with gender dysphoria.** Many in the medical profession and the media continue to represent the off-label use of puberty blockers as “well established” and “lifesaving.” Medical professionals and some journalists have refuted these statements but there is currently no single
authoritative rebuttal. While the FDA has taken an aggressive stance against medical misinformation in other contexts, it has done nothing to counter these misrepresentations. The public deserves the truth from its government about the potential harms of these drugs and the lack of established benefit.

The FDA can address the misinformation surrounding the off-label use of puberty blockers in children by commissioning a systematic review of existing peer-reviewed studies by NASEM with the goal of developing an authoritative assessment of the evidence, as has been conducted by health authorities in the UK, Sweden, and Finland. The scope of the review should, at a minimum, cover the safety issues discussed in this petition—effects of puberty blockers on bone density, fertility, and neurocognitive development—their effectiveness in treating gender dysphoria, and whether puberty blockers affect the suicidality of children with gender dysphoria.

Given the disension within the medical community and the charged political landscape surrounding the treatment of children with gender dysphoria, it is critical that the entire process be transparent and free from even the appearance of bias. Panelists should come from a range of relevant disciplines and have a range of practical experience; a history of questioning the gender affirming model should not bar any otherwise qualified candidate from participating on the panel. Crucially, all panelists must be free from financial conflicts of interest, and the study should not receive funding from any pharmaceutical company. The intent to conduct the review, the process of selecting panelists, and their conflict statements should be public, and the FDA should publish the report of the review on www.FDA.gov.

Upon its publication, the FDA should evaluate the NASEM report to determine whether it meets the standard for “new safety information” under section 505-1(b)(3) of the FDC Act, requiring changes to the labeling of puberty blockers under section 505(o) and relevant regulations. Specifically, the FDA should evaluate whether the information warrants action under 21 C.F.R. § 201.80(e), which provides:

A specific warning relating to a use not provided for under the “Indications and Usage” section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box.

Following publication of the NASEM report, the FDA should determine whether to require warnings related to the serious risks discussed in this petition or other risks, and disclosure that there is a lack of substantial evidence of effectiveness for the use of puberty blockers to treat children with gender dysphoria.

2. **Issue written requests under the BPCA for long-term registry studies.** Besides commissioning a NASEM systematic review of existing evidence, the FDA should also pursue long-term studies of the off-label use of puberty blockers. Recognizing that manufacturers who benefit from off-label sales of drug may never seek FDA approval, Congress enacted the BPCA to incentivize further study of pediatric uses of drugs. The BPCA provides a six-month period of marketing exclusivity to manufacturers who agree, upon a written request from the FDA, to perform studies “relating to the use of the drug in the pediatric population,” including studies of the drug’s safety and effectiveness for an off-label use. This authority is tailor-made for the current circumstance of rampant off-label use of puberty blockers in children.
Each of the issues described above—potential interference with bone density, normal neurocognitive development, and fertility; unknown effectiveness—are appropriate for further study under a BPCA written request. Ongoing Federally funded studies are too short, or otherwise inadequate. For example, in 2015, NIH announced a large grant to investigators at four gender clinics to study two groups of patients—young adolescents receiving puberty blockers and older adolescents receiving cross-sex hormones. The investigators have not yet published results for the cohort receiving puberty blockers; however, the initial publication concerning adolescents receiving cross-sex hormones is flawed: besides lacking a control group, the study follows only two of eight pre-identified endpoints, and the short time frame of the study precludes a meaningful assessment of the effectiveness of interventions that can cause lifelong changes. These limitations do not bode well for future publication concerning the puberty blocker cohort.

Long-term data is critically important and sorely missing. A full understanding of the risks and benefit of puberty blockers may require years of study to assess the effect of puberty blockers on the physical health and mental well-being of young people. We therefore urge the FDA to use its authority under the BPCA to request the development of a drug registry to track pediatric use of puberty blockers while respecting users’ privacy and anonymity. Registries can support meaningful studies of outcomes for children with gender dysphoria prescribed puberty blockers, including the rates of desistance from further treatment and rates of persistence, rates of detransition, and long-term health and well-being. This information is desperately needed to inform a robust, science-based discussion about the best model for treating a group of children who often have multiple emotional and developmental challenges. Requests to pharmaceutical companies for registry studies under the BPCA should be made public on www.FDA.gov, and the FDA should provide regular status updates about these requests.

3. **Create a dedicated web page concerning off-label use of puberty blockers.** This information and information on the NASEM study should appear on a page of www.FDA.gov that is dedicated to the off-label use of puberty blockers to treat gender dysphoria. The page should prominently disclose that this use remains off-label and should discuss the known and potential risks of this use and the uncertain benefit. The web page can serve as a clearinghouse for up-to-date, unbiased information about this off-label use, including detailed, up-to-date information about the status of written requests for studies by the FDA under the BPCA. Creating a centralized authoritative source of information will help to counter widespread confusion and misinformation about this use.

4. **Alert prescribers and industry to the consequences of unlawful promotions.** Pharmaceutical companies that promote their drugs for off-label uses have paid multi-million-dollar settlements to avoid civil and criminal judgments. But the potential for harm to users doesn’t depend on who runs the ad: off-label promotions by practitioners that oversell the benefits of an off-label use and fail to disclose the risks have the same potential to deceive consumers. We ask the FDA to notify anyone promoting puberty blockers for use in children with gender dysphoria of the potential legal consequences of off-label promotions. To deter future unlawful promotion, the FDA should also issue a statement on its web page, notifying the public that the FDA has not approved puberty blockers to treat gender dysphoria in children, and that such promotions are unlawful, whether run by manufacturers or providers.

We are also concerned by the role pharmaceutical companies play in promoting transgender identity to children and encouraging healthcare providers to medicalize distressed young people. For example, AbbVie partnered with the GenderCool Project, a project that “works toward the promotion, elevation,
and acceptance of transgenderism and non-binary sexuality among children.” Pfizer and the trade group PhRMA fund the Health Equality Index, a scorecard developed by the activist organization Human Rights Campaign to rate hospitals—including children’s hospitals—on their adoption of policies that promote “equitable and inclusive care for LGBTQ+ patients and their families.” This scorecard punishes hospitals for failing to provide puberty blockers, cross-sex hormones, and “gender affirming” surgical procedures to gender dysphoric youth on the same terms as they provide those drugs and procedures to other patients. Though these actions stop short of direct promotion, drug companies can and should be held accountable for actions that show an intent to market their drugs for an off-label use. The FDA has noted that evidence of such intent:

may include a firm’s knowledge that a healthcare provider has used or prescribed the firm’s medical product that is approved, cleared, granted marketing authorization, or exempted from premarket notification for an unapproved use, and may include activities that are not strictly promotional in nature. In short, direct promotion of this use is not necessary to establish intended use.

We ask that you review the activities of manufacturers of puberty blockers to determine their role in promoting drug use in children with gender dysphoria and issue a Letter to Industry alerting manufacturers of the consequences of unlawfully promoting this off-label use.

These actions are not intended to be exhaustive. The FDA has broad authority, not only as a regulator, but as a public health leader with powers to educate the public and convene and persuade stakeholders of the need for action. This leadership is badly needed here, where the future of a vulnerable group of children is at stake. As the number of children with gender dysphoria grows, health authorities worldwide reject the affirmative model, and states intervene to ban or limit so-called gender affirming care, we are witnessing a medical scandal unfold. We ask the FDA to act now to limit the scope of this emerging crisis.

ENVIRONMENTAL IMPACT

The actions requested are categorically excluded from the requirement to prepare an environmental assessment because the requested actions would not increase the use of the active moiety(ies) that are the subject of this petition.

ECONOMIC IMPACT

Will be submitted upon request.
CERTIFICATIONS

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

Respectfully submitted:

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According to the DSM 5, the American Psychiatric Association’s diagnostic handbook, a diagnosis of gender dysphoria is appropriate when an individual presents with:

[a] marked incongruence between one’s experienced/expressed gender and assigned gender, of at least six months’ duration, as manifested by at least two or more of the following:

- A marked incongruence between one’s experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
- A strong desire to be rid of one’s primary and/or secondary sex characteristics because of a marked incongruence with one’s experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
- A strong desire for the primary and/or secondary sex characteristics of the other gender
- A strong desire to be of the other gender (or some alternative gender different from one’s assigned gender)
- A strong desire to be treated as the other gender (or some alternative gender different from one’s assigned gender)
- A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one’s assigned gender)
- The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.


Robin Respaut and Chad Terhune, “Putting Numbers on the Rise in Children Seeking Gender Care,” Reuters, October 6, 2022, available at https://tinyurl.com/yk4w2e3x. The FDA generally divides this age group between children (age 2 to less than 12 years) and adolescents (age 12 to less than 17 years). For simplicity, this petition uses the term “child” or “children” to refer to include individuals in both groups.

This trend is not limited to the United States. European countries have been tracking the rise for decades. For example, referrals to the UK’s Gender Identity Development Service (GIDS), the largest pediatric gender clinic in the world, increased from 77 to 2590 in the years from 2009/2010 to 2018/2019. See, e.g., Gender Identity Development Service, “Referrals to the Gender Identity Development Service (GIDS) level off in 2018-19,” available at https://tinyurl.com/24ck7uhm.

An overview of the affirmative model, or so-called “gender affirming care”—and the benefits, harms, and uncertainties about this care model—appears on the website of the Society for Evidence-Based Gender Medicine (SEGM). See www.SEGM.org.


Reuters found a total of 4780 adolescents received puberty blockers in the years covered by its analysis, but notes that the tally is “likely an undercount because [it] didn’t include treatment that wasn’t covered by insurance and [was] limited to pediatric patients with a gender dysphoria diagnosis. Practitioners may not log this diagnosis when prescribing treatment.” Respaut and Terhune, supra n.2. FDA’s own analysis of data from its Sentinel system shows a dramatic increase in the use of a common puberty blocker in children ages eighteen and under between
the years 2000 and 2016. See New Pediatric Users of Leuprolide Acetate, August 17, 2017, available at https://tinyurl.com/2ur4nm6 (https://perma.cc/T9KZ-CBX4). While some of this increase reflects growth of the Sentinel system during this period, the number of “eligible members” in the system increased by roughly three to four-fold, compared to an increase from twenty-six users of leuprolide acetate in 2000 to 421 in 2016. For each year, the total number of leuprolide acetate users under age 18 significantly exceeds the number of leuprolide acetate users under age 18 with a diagnosis of central precocious puberty, suggesting the increase in incidence of gender dysphoria partially accounts for the dramatic increase in use.


8 The World Professional Association for Professional Health (WPATH), the lead organization for setting global standards for the care of individuals who identify as transgender, recently published its Standards of Care, which provides criteria for prescribing puberty blockers. The criteria include that “[t]he adolescent has reached Tanner stage 2 of puberty.” This is an early stage of puberty, generally beginning between ages nine and eleven. E. Coleman, et al. (2022) Standards of Care for the Health of Transgender and Gender Diverse People, Version 8 (“WPATH 8”), *International Journal of Transgender Health*, 23, available at https://doi.org/10.1080/26895269.2022.2100644.

9 For example, a Planned Parenthood ad that first aired in 2022 depicts two cartoon teenagers speaks directly to potential users, stating: “[p]uberty blockers are safe and can give you more time to figure out what feels right for you, your body, and your gender identity,” and “[y]our gender identity is real. You should be the one to decide what changes you want to make to your body.” See https://tinyurl.com/7pva58sx (https://perma.cc/2EBE-5AUV).


13 See Highlight of Prescribing Information, Lupron Depot-Ped, supra n.10.

14 The analysis commissioned by *The New York Times* noted only two small studies on bone density in transgender identified teenagers after ending treatment:

   In both studies, dozens of patients started blockers at 14 or 15, on average, and began estrogen or testosterone at 16. The participants, followed in one study through age 18, and in the other through age 22, saw their bones strengthen, on average, once on hormones. Still, most patients continued to lag behind their peers; trans men neared average levels, but trans women fell far below.

See Twohey and Jewett, supra n.12.
Children with gender dysphoria may desist in identifying with the opposite sex or may persist. An overview of studies of such children who were prescribed puberty blockers found that “roughly 98% of children who take [puberty blockers] go on to take cross-sex hormones.” See https://statsforgender.org/puberty-blockers/ (https://perma.cc/U8A7-8RUW). In contrast, studies of gender dysphoric children who experience normal puberty have found high rates of desistance. See Desistance - Stats For Gender (https://perma.cc/8WDE-H8WA); see also Zucker, K. J. (2018), The Myth of Persistence, International Journal of Transgenderism 19 (2): 231-45, available at https://doi.org/10.1080/15532739.2018.1468293.

See WPATH 8, supra n 8.


See https://tinyurl.com/5sx2u5h44 (https://perma.cc/3MKX-URZT).


See Biggs, Dutch Protocol Critique, supra n.7.

Id. A similar complication occurred in an American teenager whose male puberty was blocked, leading to “severe” complications in the surgery to create a neovagina from existing genital tissue. See Clark Sparky, “Jazz Jennings And Her Doctors Reveal The 'Severe Complications' From Her Gender Confirmation Surgery,” Yahoo News, available at https://tinyurl.com/2s4zrb8h (https://perma.cc/AJ2U-EZ27).


See National Institute for Health and Care Excellence (2020) Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria, available at https://tinyurl.com/45pn8iy9 (https://perma.cc/79WJ-HM55). The review covered nine studies that met review criteria, including the first of the two foundational Dutch studies. The review excluded the second Dutch study because the exclusion criteria disallowed multiple studies with the same population.

Id.

28 See Ann P. Haas, Ph.D., Philip L. Rodgers, Ph.D., and Jody L. Herman, Ph.D., Suicide Attempts among Transgender and Gender Non-Conforming Adults: Findings of The National Transgender Discrimination Survey (2014), Williams Institute, American Foundation for Suicide Prevention, available at https://tinyurl.com/2s36x8n4.

29 See id. at 3 (noting the methodology used has been found to inflate reports of suicide attempts, among other limitations.)


33 See Press Release, AMA strengthens its policy on protecting access to gender-affirming care, available at https://tinyurl.com/5n95ea4f (https://perma.cc/MS44-NSTF) (noting multiple medical organizations supporting an Endocrine Society resolution to support gender affirming care.)


40 See Juliana Bunum, “First U.S. Study of Transgender Youth Funded by NIH,” available at https://tinyurl.com/5359y3c4 (https://perma.cc/7CVQ-DA5). The co-investigators include Johanna Olson, MD, Children’s Hospital Los Angeles and the Keck School of Medicine of the University of Southern California; Stephen Rosenthal, MD, UCSF Benioff Children’s Hospital San Francisco; Robert Garofalo, MD, MPH, Ann & Robert H. Lurie Children’s Hospital of Chicago and Northwestern University Feinberg School of Medicine; and Norman Spack, MD, Boston Children’s Hospital and Harvard Medical School.


44 For example, a hospital in Texas lost points on the index because it denied a hysterectomy to a trans-identified female, who sought the procedure to treat her gender dysphoria. See Sibarium, id.


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