ETHICS AND PUBLIC POLICY CENTER

April 7, 2025

Via Federal eRulemaking Portal

Kimberlee Trzeciak
Deputy Commissioner for Policy, Legislation, and International Affairs
Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20852

RE: FDA Notice "Study of Sex Differences in the Clinical Evaluation of Medical Products; Draft Guidance for Industry; Availability," Docket No. FDA-2024-D-4245

Dear Deputy Commissioner Trzeciak:

I am a scholar at the Ethics and Public Policy Center (EPPC), director of EPPC's Administrative State Accountability Project (ASAP), and a former attorney at the Equal Employment Opportunity Commission. I write in response to the Food and Drug Administration's (FDA) January 7, 2025, notice "Study of Sex Differences in the Clinical Evaluation of Medical Products; Draft Guidance for Industry; Availability."[1]

The notice announces draft guidance that "provides recommendations for increasing enrollment of females in clinical trials, analyzing and interpreting sex-specific data, and including sex-specific information in regulatory submissions of medical products."[2] It would replace the 1993 guidance entitled "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs." The notice does not explain why the 1993 guidance is inadequate, and I take no position on whether an updated guidance is needed.

I write to support the importance of studying sex differences in the clinical evaluation of medical products and to draw the FDA's attention to ways that the draft guidance is inaccurate and conflicts with President Trump's executive orders and Department of Health and Human Services (HHS) guidance.

A. Sex-Related Differences Matter

As the draft guidance states, "[h]istorically, fewer females than males have been included in clinical trials of medical products, which has led to a lack of information available for females and their health care providers regarding the benefits and risks of such medical products in females."[3] The notice explains that "[a]nalyzing sex-related differences in medical product response is an important component of assessing and understanding product safety and effectiveness."[4] This can help improve patient care because "differences in

[1] 90 Fed. Reg. 1132 (Jan. 7, 2025), https://www.federalregister.gov/d/2024-31537.
[2] *Id.* at 1132.
[3] FDA, HHS, Study of Sex Differences in the Clinical Evaluation of Medical Products Guidance for Industry: DRAFT GUIDANCE, Jan. 2025, at 4-5 [hereinafter "Draft Guidance"], *available at* https://www.regulations.gov/document/FDA-2024-D-4245-0002.
[4] 90 Fed. Reg. at 1132.

physiology between females and males can lead to differences in disease manifestation, pharmacokinetics, pharmacodynamics, and response to treatment, among other things."[5]

I agree that it is important to study sex differences in the development and clinical evaluation of medical products because biological and physiological differences between males and females could impact efficacy and safety. I also support the consideration, when relevant, of factors that are unique to women—like menstrual cycles, menopause, pregnancy, and lactation. With this consideration, due weight should be given to any risks or harm to the life and health of a mother and her unborn child.

As the HHS Office on Women's Health acknowledges, "[r]ecognizing the immutable and biological nature of sex is essential to ensure the protection of women's health [and] safety[.]"[6] Women are not just small men. Information about a medical product's impact on females is necessary for a woman to fully appreciate the benefits and risks and make informed decisions about her health.

B. The Draft Guidance's Discussion of Sex and Gender Is Inaccurate

The draft guidance's discussion of sex and gender is inaccurate and should be corrected in any final guidance.

Of relevance, the terminology section states:

> While, over time, the terms sex and gender have often been used interchangeably in the scientific literature, media, and FDA guidance and regulations, the constructs of sex and gender have evolved into separate concepts with distinct definitions that should be used consistently in the design, conduct, analysis, and reporting of data from clinical trials and non-interventional studies submitted to FDA. For the purposes of this guidance, the following definitions are used to distinguish sex and gender:
>
> - **Sex** is a biological construct based on anatomical, physiological, hormonal, and genetic (chromosomal) traits. Sex is generally assigned based on anatomy at birth and is usually categorized as female or male, but variations occur. Variations of sex refers to differences in sex development or intersex traits.
>
> - **Gender** is a multidimensional construct that encompasses how an individual self-identifies. Gender may be described across a continuum, may be nonbinary, and may change over the course of a lifetime. Gender may or may not correspond to a person's sex assigned at birth.
>
> For many drug and device trials, the term gender is used as a substitute for biological sex. In most cases, a participant's sex and gender are concordant, but FDA recognizes that sex and gender are not always concordant. Although sex and gender are distinct concepts, they may both influence etiology and presentation of disease and affect treatment and patient-reported outcomes. This guidance focuses on biological differences that can impact outcomes in clinical trials and non-interventional studies and therefore focuses on sex. However, FDA also encourages sponsors to consider whether gender differences are relevant to a specific study and should be factored into the study design and analysis.
>
> For the purposes of this guidance, we use the terms *male* and *female* to refer to biological sex assigned at birth, and *male* and *female* will represent distinct biological categories. It may be

[5] *Id.*
[6] *See* HHS, *Sex-Based Definitions*, https://womenshealth.gov/article/sex-based-definitions (last updated Feb. 19, 2025).

> appropriate to include a separate category for intersex in clinical trials and non-interventional studies and to collect data on individuals for whom the development of chromosomal, gonadal, or anatomic sex is atypical. Further discussion of the inclusion of intersex individuals is beyond the scope of this guidance.[7]

The next two sections on data standards and representation of female participants in clinical trials and non-interventional studies contain the following relevant statements:

- "For trial data submitted to FDA, the *sex* variable should reflect the *sex assigned at birth* of each participant to be consistent with the CDISC definition."[8]
- "FDA recommends that participants (not the team conducting the trial) self-report sex information, which is generally based on their *sex assigned at birth*."[9]
- "FDA encourages inclusion of gender data particularly if gender may influence the outcome of interest. FDA recommends discussing the incorporation of data on gender with the appropriate review division."[10]
- "While the 1993 guidance uses the term *women* when referring to female sex, this guidance uses the term *female*."[11]

The discussion of sex and gender in these sections is inaccurate in multiple ways.

First, the draft guidance falsely states that sex is a construct. Sex is a biological reality, not a construct.

Second, sex is not "assigned at birth." It is determined at conception and cannot change.[12] While sex is often observed at birth, it can also be determined prior to birth through genetic testing or an ultrasound.

Third, there are only two sexes: male and female.[13] There is no third sex. Those who have a disorder of sexual development (DSD) (often referred to as "intersex") are still either male or female.[14] To the extent that a DSD would impact the efficacy and safety of a medical product, the person's DSD should be considered, but this consideration should be based on the relevant impact of the specific DSD, not the false notion that individuals with a DSD are a "third sex."

Fourth, "gender" as defined in the draft guidance has no place in the clinical evaluation of medical products. A subjective, self-identified, and changing label that has no connection to any objective criteria does not provide meaningful information about its impact on individuals who identify similarly. The FDA should not encourage the inclusion or incorporation of "gender data."

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[7] Draft Guidance at 5-6 (citations omitted).
[8] *Id.* at 7 (emphasis added).
[9] *Id.* (emphasis added).
[10] *Id.*
[11] *Id.*
[12] *See* HHS, *Sex-Based Definitions*, https://womenshealth.gov/article/sex-based-definitions (last updated Feb. 19, 2025) ("The sex of a human, female or male, is determined genetically at conception (fertilization), and is observable before birth…. A person's sex is unchangeable and determined by objective biology.").
[13] *See id.* ("There are only two sexes, female and male, because there are only two types of gametes. An individual human is either female or male based on whether the person is of the sex characterized by a reproductive system with the biological function of producing eggs (ova) or sperm.").
[14] *See id.* ("Rare disorders of sexual development do not constitute a third sex because these disorders do not lead to the production of a third gamete.").

Fifth, the guidance asserts without citation that gender "may influence etiology and presentation of disease and affect treatment and patient-reported outcomes." Declaring oneself to be a certain gender does not change one's disease and treatment profile.

Sixth, the guidance implies that women are not necessarily female.[15] This is false. Women are adult human females, and to imply that a male can be a woman by self-identifying that way is insulting and wrong.

In sum, in any final guidance, the terminology section should be deleted in its entirety, the references to "sex assigned at birth" should be dropped (just saying sex would be sufficient), the FDA should not encourage the inclusion or incorporation of "gender data," and the FDA should not imply that males can be women.

C. The Draft Guidance's Discussion of Sex and Gender Conflicts with President Trump's Executive Orders and HHS Guidance

The draft guidance's discussion of sex and gender is reflective of the Biden-Harris administration's promotion of gender ideology. On day one, President Trump revoked multiple Biden-era executive orders directing the federal government to promote gender ideology, including:

- Executive Order 13985 on "Advancing Racial Equity and Support for Underserved Communities Through the Federal Government" (Jan. 20, 2021);
- Executive Order 13988 on "Preventing and Combating Discrimination on the Basis of Gender Identity and Sexual Orientation" (Jan. 20, 2021); and
- Executive Order 14075 on "Advancing Equality for Lesbian, Gay, Bisexual, Transgender, Queer, and Intersex Individuals" (June 15, 2022).[16]

The same day, President Trump also issued an executive order entitled "Defending Women from Gender Ideology Extremism and Restoring Biological Truth to the Federal Government."[17] I specifically direct you to the following aspects of the President's Executive Order:

- Section 2(a) recognizes "sex" as "an individual's immutable biological classification as either male or female" and "not a synonym for and does not include the concept of 'gender identity.'"
- Section 2(b) recognizes "women" and "girls" as "adult and juvenile human females, respectively."
- Section 2(c) recognizes "men" and "boys" as "adult and juvenile human males, respectively."
- Section 2(d) recognizes that a "female" is "a person belonging, at conception, to the sex that produces the large reproductive cell."
- Section 2(e) recognizes that a "male" is "a person belonging, at conception, to the sex that produces the small reproductive cell."

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[15] This implication is made explicit in another FDA draft guidance proposed on January 7, 2025. *See* FDA, HHS, Evaluation of Sex-Specific and Gender-Specific Data in Medical Device Clinical Studies: Draft Guidance for Industry and FDA Staff, Jan. 2025, at 2-3, *available at* *https://www.regulations.gov/document/FDA-2023-D-5591-0002* ("Use of the term male and female versus man and woman depends upon whether biological or psychosocial factors are under study. For purposes of this document, the terms male and female are used in the context of sex. The terms man, woman, nonbinary and/or transgender are used in the context of gender.").

[16] 90 Fed. Reg. 8237 (Jan. 28, 2025), https://www.federalregister.gov/d/2025-01901.

[17] 90 Fed. Reg. 8615 (Jan. 30, 2025), https://www.federalregister.gov/d/2025-02090.

- Section 2(f) recognizes: "'Gender ideology' replaces the biological category of sex with an ever-shifting concept of self-assessed gender identity, permitting the false claim that males can identify as and thus become women and vice versa, and requiring all institutions of society to regard this false claim as true. Gender ideology includes the idea that there is a vast spectrum of genders that are disconnected from one's sex. Gender ideology is internally inconsistent, in that it diminishes sex as an identifiable or useful category but nevertheless maintains that it is possible for a person to be born in the wrong sexed body."

- Section 2(g) recognizes that "'Gender identity' reflects a fully internal and subjective sense of self, disconnected from biological reality and sex and existing on an infinite continuum, that does not provide a meaningful basis for identification and cannot be recognized as a replacement for sex."

- Section 3(a) instructs the Secretary of HHS to "provide to the U.S. Government, external partners, and the public clear guidance expanding on the sex-based definitions set forth in this order."

- Section 3(b) states that federal agencies "shall enforce laws governing sex-based rights, protections, opportunities, and accommodations to protect men and women as biologically distinct sexes" and directs the agencies to "give the terms 'sex', 'male', 'female', 'men', 'women', 'boys' and 'girls' the meanings set forth in [the] order when interpreting or applying statutes, regulations, or guidance and in all other official agency business, documents, and communications."

- Section 3(c) directs that "[w]hen administering or enforcing sex-based distinctions," federal agencies "shall use the term 'sex' and not 'gender' in all applicable Federal policies and documents."

In response to President Trump's executive orders defending women and children, HHS announced on February 19, 2025, that it was launching a webpage "to promote guidance on sex-based definitions and other resources on efforts to protect women and children."[18] As Dorothy Fink, MD, Deputy Assistant Secretary for Women's Health, explained, "HHS recognizes that biological differences between females and males require sex-specific practices in medicine and research to ensure optimal health outcomes."[19]

The HHS webpage provides the following definitions:

- ***Sex*** is a person's immutable biological classification as either male or female.
- ***Female*** is a person of the sex characterized by a reproductive system with the biological function of producing eggs (ova).
- ***Male*** is a person of the sex characterized by a reproductive system with the biological function of producing sperm.
- ***Woman*** is an adult human female.
- ***Girl*** is a minor human female.
- ***Man*** is an adult human male.
- ***Boy*** is a minor human male.[20]

[18] Press Release, HHS, HHS' Civil Rights Office Takes Action to Support President Trump's Executive Orders to Protect Minors and Restore Biological Truth (Feb. 20, 2025), https://www.hhs.gov/about/news/2025/02/20/hhs-civil-rights-office-takes-action-support-president-trumps-executive-orders-protect-minors-restore-biological-truth.html.
[19] *Id.*
[20] HHS, *Sex-Based Definitions*, https://womenshealth.gov/article/sex-based-definitions (last updated Feb. 19, 2025).

These definitions conflict with the FDA's discussion of sex and gender in its draft guidance. Any final guidance should reflect these definitions and the policies in President Trump's executive orders.

Conclusion

For the reasons stated above, I urge the FDA to carefully examine its draft guidance in light of President Trump's executive orders and HHS guidance. In any final guidance, the discussion of sex and gender should be corrected. I hope this public comment helps the FDA better carry out its important responsibilities and ensure that its actions and policies reflect the President's priorities and directives.

Sincerely,

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