July 6, 2026

Submitted Electronically

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA-2026-N-2886 Comment in Strong Support of the Proposed Rule: Modification of Certain Terminology in Title 21

To Whom It May Concern:

Do No Harm is a non-profit organization with over 50,000 members, including physicians, healthcare professionals, medical students, patients, and policymakers. Our goal is to ensure that the practice of medicine is driven by scientific evidence—not political ideologies. To that end, we write in support of the FDA's proposed rule replacing "gender" with "sex," or removing "gender" altogether, throughout Title 21 of the Code of Federal Regulations ("CFR"). The proposed changes are necessary and clarifying: FDA regulations would once again be aligned with biological reality.

The change follows the directive of Executive Order 14168, "Defending Women From Gender Ideology Extremism and Restoring Biological Truth to the Federal Government," issued on January 20, 2025. Per the Executive Order: "every agency . . . shall use the term 'sex' and not 'gender' in all applicable Federal policies and documents."[1] It further directs agencies to "remove all statements, policies, [and] regulations" that "promote or otherwise inculcate gender ideology."[2] Unfortunately, these ideologies have seeped into the medical context. And the proposed change would restore scientific precision to FDA regulations.

This proposal is also sound policy, independent of any executive mandate. Scientific research depends on objective facts, not subjective beliefs. But current regulatory language references "gender," a self-reported and shifting identity, instead of "sex," a constant biological reality. Doctors and researchers should not be forced to accept falsehoods to satisfy ideological preferences. Otherwise, patients—especially women—bear the cost. The proposed rule change would yield significant improvements in drug safety, adverse-event reporting, and medical-device validation.

I. Scientific evidence supports the use of "sex," not "gender."

Sex is a primary variable that affects pharmacokinetics, *i.e.*, the movement of drugs through the body. Thus, "[i]ntegrating biological sex-specific data into clinical guidelines is essential to

[1] Exec. Order No. 14,168, § 3(c), "Defending Women From Gender Ideology Extremism and Restoring Biological Truth to the Federal Government," 90 Fed. Reg. 8615 (Jan. 30, 2025).

[2] *Id*. § 3(e).

optimize drug efficacy and minimize [adverse drug reactions]."[3] Understanding "sex-based differences in pharmacologic parameters" is essential given the impact of one's sex on both the efficacy and potential toxicity of medications.[4] The existing research makes clear that, "[m]ales and females differ in their response to drug treatment."[5] And these critical differences must be understood if one is to design treatments that are both safe and effective.[6]

The proposed changes are necessary to ensure health of women in particular. In summarizing sex differences in pharmacokinetics, research has found that "for most of the FDA-approved drugs examined, elevated blood concentrations and longer elimination times were manifested by women, and these [pharmacokinetics] were strongly linked to sex differences in [adverse drug reactions]."[7] Therefore, "[t]he common practice of prescribing equal drug doses to women and men neglects sex differences in pharmacokinetics and dimorphisms in bodyweight, risks overmedication of women, and contributes to female-biased adverse drug reactions."[8]

Again, these differences are rooted in sex, not gender. While gender refers to social roles, cultural expectations, and an individual's subjective identity, sex is a biological classification grounded in chromosomes, gamete production, hormones, and reproductive anatomy. Sex is the measurable variable relevant to FDA's regulatory responsibilities. The scientific literature is unequivocal: sex significantly influences drug absorption, distribution, metabolism, and excretion.[9] And it is a key determinant of differential adverse reaction rates.

The same is true for medical devices. One review paper found that "some [medical devices] are less efficient in women than in men and sometimes [medical devices] are less safe for women than men."[10] The FDA has already provided guidance on the "study and evaluation of sex-specific data in medical device clinical studies."[11] The guidance document emphasized

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[3] Aljohmani A, Yildiz D. Biological sex differences in pharmacokinetics and adverse drug reactions. Naunyn Schmiedebergs Arch Pharmacol. 2026 Feb;399(3):3285-3301. doi: 10.1007/s00210-025-04721-8. Epub 2025 Oct 21. PMID: 41117965; PMCID: PMC12935741. https://pubmed.ncbi.nlm.nih.gov/41117965/.

[4] Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and pharmacodynamics. Annu Rev Pharmacol Toxicol. 2004;44:499-523. doi: 10.1146/annurev.pharmtox.44.101802.121453. PMID: 14744256. https://pubmed.ncbi.nlm.nih.gov/14744256/.

[5] Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 2009;48(3):143-57. doi: 10.2165/00003088-200948030-00001. PMID: 19385708; PMCID: PMC3644551. https://pmc.ncbi.nlm.nih.gov/articles/PMC3644551/.

[6] *Id.*

[7] Zucker I, Prendergast BJ. Sex differences in pharmacokinetics predict adverse drug reactions in women. Biol Sex Differ. 2020 Jun 5;11(1):32. doi: 10.1186/s13293-020-00308-5. PMID: 32503637; PMCID: PMC7275616. https://pubmed.ncbi.nlm.nih.gov/32503637/.

[8] *Id.*

[9] Aljohmani & Yildiz, *supra* note 3.

[10] Campesi I, Franconi F, Serra PA. The Appropriateness of Medical Devices Is Strongly Influenced by Sex and Gender. Life (Basel). 2024 Feb 7;14(2):234. doi: 10.3390/life14020234. PMID: 38398743; PMCID: PMC10890141. https://pubmed.ncbi.nlm.nih.gov/38398743/.

[11] U.S. Food and Drug Administration, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research. *Evaluation of Sex-Specific Data in Medical Device Clinical Studies: Guidance for Industry and Food and Drug Administration Staff*. Docket No. FDA-2011-D-0817. Issued March 31, 2025 (originally issued August 22, 2014). https://www.fda.gov/media/82005/download.

differences in "genetics, hormones, body size, and sex-specific physiology" between men and women.[12]

Other regulatory bodies also emphasize the importance of sex, not gender. Since 2016, the NIH has required that "sex as a biological variable . . . be factored into research designs, analyses, and reporting in vertebrate animal and human studies."[13] A "strong justification" is required for any study of only one sex.[14] NIH adopted this policy in part because "an over-reliance on male animals and cells may obscure understanding of key sex influences on health processes and outcomes."[15] The Institute of Medicine's landmark 2001 report said succinctly: "every cell has a sex," and urged further study of sex-based differences "from womb to tomb."[16]

II. The specific changes to the CFR are aligned with these scientific principles.

The proposal modifies sixteen parts of the CFR. Some of these provisions indiscriminately use "sex" and "gender," resulting in a muddled regulatory landscape. The proposed changes would clarify FDA protocols, more closely aligning them with scientific principles. Below we explain the benefit of ensuring the proper use of the term sex in the various contexts that will be modified by the proposed rule: clinical studies, prescription labeling, adverse-event reporting, device regulation, infant-formula testing, and IRB membership.

Clinical Studies.[17] Several provisions require clinical trials to tabulate enrollment and outcomes by subgroup. Currently, those provisions specify "gender," not sex. But calling this variable "gender" invites confusion about what is being measured. A clinical trial should stratify data based on biological sex—the chromosomal, hormonal, and physiological characteristics driving pharmacokinetic variation.

Prescription labeling.[18] The FDA requires labels to include specific information to ensure safe dosing recommendations. Currently, the Code lists "gender" as one of the significant factors affecting pharmacokinetics. But, as explained above, "gender" does not affect how pharmaceuticals interact with the body. Sex does.

And the Code already references "sex" in the context of contraindication requirements. Specifically, labels are required to specify subpopulations who "have a substantial risk of being

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[12] *Id.*

[13] National Institutes of Health. *Consideration of Sex as a Biological Variable in NIH-funded Research*. NOT-OD-15-102. 2015. https://grants.nih.gov/grants/guide/notice-files/not-od-15-102.html.

[14] *Id.*

[15] National Institutes of Health, Office of Research on Women's Health. *Sex as a Biological Variable*. https://orwh.od.nih.gov/sex-as-biological-variable.

[16] Wizemann TM, Pardue ML, eds. *Exploring the Biological Contributions to Human Health: Does Sex Matter?* Institute of Medicine, Committee on Understanding the Biology of Sex and Gender Differences. Washington, DC: National Academies Press; 2001. doi:10.17226/10028.

[17] 21 C.F.R. 312.33(a)(2) (annual IND reports); 21 C.F.R. 314.50 (underlying subgroup-analysis requirements).

[18] 21 C.F.R. 201.57(c)(13)(i)(C).

harmed by the drug and for whom no potential benefit makes the risk acceptable."[19] Changing gender to sex in the other provision would render the Code more coherent and consistent.

Adverse Event Reporting.[20] Pharmaceutical companies have an ongoing duty to ensure the safety of their products—even after clinical testing and market approval. To enforce that duty, the Code currently mandates reporting of adverse events. Such reports must separate patients by sub-categories, including "gender." This stratification monitors drug safety across different populations. There are many situations illustrating the importance of stratifying *based on sex*. For example, take terfenadine and cisapride. Both drugs were withdrawn from the market because they posed an increased risk to women of torsades de pointes, a potentially fatal cardiac arrhythmia.[21] Another example is zolpidem, the most prescribed sleep medication in the U.S.[22] In 2013, the FDA announced the recommended dosage for women was to be reduced by 50%, due to newly discovered effects.[23]

Device regulations.[24] The FDA also requires safety studies for diagnostic devices, including vitamin D mass spectrometry test systems, sepsis biomarker assays, and genetic health risk assessment systems. Such studies must reflect demographic characteristics "representative of the U.S. population," including "gender" distribution. But demographic representativeness matters only insofar as subpopulations react differently to the devices. Thus, the key distinction, as explained above, is between the two sexes—men and women.

Infant Formula Testing.[25] The Code currently requires that studies be conducted on infant formulas. Such studies must report on a variety of identifiers, including "gender." But infants cannot have a "gender identity" that differs from their sex. Nor would data based on "gender," in addition to sex, offer any meaningful scientific insight. This rule change is thus sensible, connecting the guidelines to reality.

IRB membership.[26] An IRB must have a "diversity of . . . members."[27] But the current provision includes references to both "sex" and "gender." Specifically, the Code mandates that "[e]very nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so

[19] 21 C.F.R. 201.57(c)(5).

[20] 21 C.F.R. 803.32, 803.42, 803.52 (submitted by user facilities, importers, and manufacturers); 21 C.F.R. 314.80, 310.305, 329.100, 600.80 (postmarketing reports).

[21] Heinrich J. *Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women*. United States General Accounting Office; 2001. GAO-01-286R. https://www.gao.gov/assets/gao-01-286r.pdf

[22] Kane SP. Zolpidem. *ClinCalc DrugStats Database*, Version 2025.08. Prescription data source: Medical Expenditure Panel Survey (MEPS) 2014-2023, Agency for Healthcare Research and Quality (AHRQ), Rockville, MD. Updated August 10, 2025. https://clincalc.com/DrugStats/Drugs/Zolpidem

[23] U.S. Food and Drug Administration. *Drug Safety Communication: Risk of Next-Morning Impairment After Use of Insomnia Drugs; FDA Requires Lower Recommended Doses for Certain Drugs Containing Zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist)*. January 10, 2013. https://www.fda.gov/files/drugs/published/Drug-Safety-Communication--Risk-of-next-morning-impairment-after-use-of-insomnia-drugs--FDA-requires-lower-recommended-doses-for-certain-drugs-containing-zolpidem-(Ambien--Ambien-CR--Edluar--and-Zolpimist).pdf

[24] 21 C.F.R. 862.1840, 866.3215, 866.5950.

[25] 21 C.F.R. 106.121(a)(2).

[26] 21 C.F.R. 56.107.

[27] 21 C.F.R. 56.107(a).

long as no selection is made to the IRB on the basis of gender."[28] Given the canon of meaningful variation, the two words, "sex" and "gender," presumptively carry different meanings.[29] But the provision is nonsensical if that is true. And the text of the provision is clearly focused on preventing *sex* discrimination. Thus, the proposed rule's change would help clarify any ambiguity in interpreting this provision.

III. Conclusion

The Executive Order emphasized that "[i]nvalidating the true and biological category of 'woman'" undermines "laws and policies designed to protect sex-based opportunities."[30] At stake here is not just "sex-based opportunities[,]" but women's health. The safety and efficacy of medical treatments should not be sacrificed in furtherance of gender ideologies. We thus write in strong support of the proposed changes.

Sincerely,

Dr. Stanley Goldfarb
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[28] 21 C.F.R. 56.107(b).
[29] *See, e.g.*, *Pulsifer v. United States*, 601 U.S. 124, 151 (2024).
[30] Exec. Order No. 14,168, § 1, 90 Fed. Reg. 8615 (Jan. 30, 2025).