The Fate Of Biden-Era Clinical Study Guidance Under Trump

By **Eva Temkin, Phil Desjardins and Liz Lindquist** (February 21, 2025)

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Among the flurry of U.S. Food and Drug Administration guidance documents issued in early January by the outgoing Biden Administration were two guidance drafts addressing the study and evaluation of sex and gender differences in medical product development: "Study of Sex Differences in the Clinical Evaluation of Medical Products"[1] and "Evaluation of Sex-Specific and Gender-Specific Data in Medical Device Clinical Studies."[2]

Both of these draft guidance documents, in addition to the FDA's statutorily required guidance on diversity action plans, or DAPs, were intended to provide recommendations for sponsors developing new products that may be required to submit information demonstrating safety and effectiveness across sexes and gender patient populations.

The DAP draft guidance more generally provided guidance to sponsors conducting studies requiring DAPs.[3]

Addressing clinical trial diversity has been a key FDA objective in recent years to address the historic underrepresentation of women and minorities in clinical studies of new drugs, biologics and devices — and to ensure that clinical data supporting regulatory decision-making is representative of likely users of approved products.

The FDA defined sex, for purposes of the draft guidance documents, to mean a biological construct based on anatomical, physiological, hormonal and genetic traits, referred to as male and female.

Gender, on the other hand, was defined as a multidimensional construct encompassing self-identification across a continuum that may or may not correspond to a person's sex, and may be nonbinary or fluid for a person over time.

At the time the draft guidance documents were published, it was not expected that the recommendations in either guidance would raise significant concern given the scientific community's general acceptance that a well-controlled clinical trial must enroll a representative population to ensure the new product is studied in subjects of all backgrounds.

In fact, the FDA believed so strongly in this that the guidance drafts in effect put sponsors on notice of the FDA's commitment to considering representative enrollment of patients across sexes in clinical trials, and even potentially placing clinical investigations under investigational new drug applications or investigational device exemptions on clinical hold or take other actions, e.g., requiring post-approval studies, when studies do not adequately enroll patients from both sexes.

However, on Day 1 of the new administration, President Donald Trump issued an executive order stating that, as a matter of policy, there are only two sexes: male and female.

Similarly, the executive order restricted agencies from using the term "gender," stating that "[s]ex is not a synonym for and does not include the concept of 'gender identity.'"

The executive order went on to define "male" and "female" based on the person's "belonging, at conception, to the sex that produces" either the large reproductive cell, i.e., egg, or the small reproductive cell, i.e., sperm.[4]

It also ordered "agencies [to] remove all statements, policies, regulations, forms, communications, or other internal and external messages that promote or otherwise inculcate gender ideology."

Presumably in light of this, by Jan. 23, the sex differences draft guidance, DAP draft guidance, and sex- and gender-specific data draft guidance had been removed from the FDA's website, ostensibly as a result of new scrutiny in light of the Trump administration's executive orders rolling back actions on diversity, equity and inclusion, and reversing positions with respect to sex and gender.[5][6]

Shortly thereafter, these and related availability changes by the FDA were challenged in a **lawsuit** filed by Doctors for America in the U.S. District Court for the District of Columbia on Feb. 4 against the FDA and several other federal agencies.[7]

The complaint highlights the sex differences draft guidance and DAP draft guidance as "important guidance for researchers who develop clinical trials,"[8] and argues that the FDA's removal of these guidance drafts, along with health-related data and other information used by health professionals and researchers, from publicly accessible government websites, without advance notice, as arbitrary and capricious in violation of the Administrative Procedure Act and Paperwork Reduction Act.

Doctors for America seeks, among other things, a court order requiring the FDA and U.S. Department of Health and Human Services to restore webpages and datasets that were removed.

On Feb. 11, the court granted the plaintiff's motion to temporarily restrain the FDA, as well as the Centers for Disease Control and Office of Personnel Management, from further removing or modifying health-related webpages and datasets — and to compel them to restore webpages and datasets that they have already removed or modified as of Jan. 30 by Feb. 11.

Notably, unlike the other two guidance drafts in question, the DAP draft guidance was specifically required by Congress as part of the clinical trial diversity and modernization provisions of the Food and Drug Omnibus Reform Act.[9]

FDORA added a clear statutory requirement that sponsors of certain clinical investigations of drugs and devices must submit a diversity action plan that includes the sponsor's goals for enrollment, the rationale for such goals and an explanation of how the sponsor intends to meet such goals.[10]

The form and manner of these diversity action plans was to be established in guidance by the FDA within a specified time period. The FDA was late issuing the draft guidance, which was issued on June 26, 2024, and had been expected to issue the final guidance in late June of this year.[11]

Importantly, the DAP requirement only applies to clinical investigations that begin enrollment more than 180 days after the publication of the final guidance.[12]

Going Forward

At this time, the situation remains in flux. The guidance documents have not been formally withdrawn by the FDA or HHS and the D.C. district court's temporary restraining order required the FDA to restore the related content that was removed from the agency's website by Feb. 11.

The comment period for the sex- and gender-specific data draft guidance is open through April 7, though we expect this may be extended in light of the litigation and subsequent reinstatement.

We summarize each of the guidance drafts below, but emphasize that this is an unusual case where the actions beyond the guidance documents speak more than the recommendations from the FDA themselves.

The removal of the documents from the website signals that the FDA is likely to tread softly in this area in the coming years, and casts doubt over the implementation and enforcement of diversity action plans and related requirements.[13]

This, in turn, raises questions for industry stakeholders, many of whom have already taken additional efforts to enroll more representative populations in clinical trials that meet the diversity action plan requirements, under the assumption that the FDA would begin enforcing those requirements in the summer.

Now that the DAP draft guidance in particular has been taken down, the FDA and stakeholders must grapple with how to move forward with the diversity action plan statutory requirements — many of which stakeholders had already been adopting as good practice in advance of the FDA's final guidance.

If the new administration prohibits the FDA from issuing such guidance, either because it views the guidance as violating the order on sex, or the executive order ending government DEI programs, then the DAP requirement arguably will not take effect.

We are also monitoring the changing landscape to see whether manufacturers that already practice principles related to clinical trial diversity may be at risk if they, for example, use federal grants to fund an investigation or rely on a National Institutes of Health clinical site.

What is more, a restriction on the FDA issuing the draft guidance will have implications on life sciences companies from a product liability standpoint.

Including robust representative populations from both sexes in clinical investigations is critical to avoiding product liability risks — risks that undoubtedly stifle innovation.

And manufacturers are facing a plaintiffs bar that is increasingly bullish about pursuing more creative and untraditional product liability theories.

As technology continues to advance in the design and development of new medical products, it is plausible that plaintiffs will bring product liability claims, including for design defect and failure to warn, based on a manufacturer's alleged failure to properly study and evaluate sex differences, gather data from an adequately diverse patient population, and

utilize diverse data sets to dictate safe and effective use of medical products for all populations.

Plaintiffs may argue that a lack of diversity in data skews outcomes and leads to treatments that are less effective. This is true for all types of medical products but could especially be a challenge for AI and machine learning enabled devices that rely on diverse data sets to make patient recommendations to healthcare providers.

With respect to those devices, plaintiffs are likely to allege that failure to study representative populations can lead to inaccurate data input and result in a significant risk of data bias and less reliable algorithm predictions.

Summary of the Evaluating Sex Differences Draft Guidance

The FDA's draft guidance concerning sex differences in the clinical evaluation of medical products is most applicable to sponsors of products conducting clinical trials, typically under investigational new drug applications, that are intended to support submission of an application, e.g., new drug applications, abbreviated new drug applications, and biologics license applications.

The draft guidance focuses on sex differences, noting that gender is not a required data variable.

Most of the FDA's recommendations are common sense, though a few may foreshadow what the FDA plans to look at when determining whether regulatory action is warranted. In order to evaluate sex differences, FDA recommends:

- Evaluating demographic distribution across different time points to assess, for example, whether inclusion criteria should be adjusted increase enrollment of females;
- Consulting places focused on women's health to help increase female enrollment and retention;
- Employing remote monitoring or other digital health technologies where appropriate; and
- In studies where exclusion of pregnant females are justified, performing pharmacokinetic sampling.

The FDA also recommends that sponsors evaluate other variables that may affect drug absorption or metabolism differently based on a person's sex, such as the person's smoking status, age or weight.

Importantly, the draft guidance is clear that the FDA intends to evaluate data disaggregated by sex when determining whether a clinical study allows for a positive benefit-risk assessment of the product.

Moreover, sponsors should be aware that the FDA is attuned to looking at whether data from males can estimate effectiveness or safety in females and vice versa based on how similar the data is based on enrollment.

Summary of the Study of Sex and Gender Differences in Medical Device Clinical Studies Draft Guidance

Similar to the sex differences draft guidance, the sex- and gender-specific data draft guidance does not significantly depart from past recommendations.

Instead, it provides insight into the FDA's likely focal points and explains why evaluating product performance across sex and gender is critical to ensuring the reasonable safety and effectiveness of medical devices approved by the FDA.

For clinical studies intended to support medical device applications and submissions, FDA recommends that specific information concerning sex and gender be included in the investigational device exemption study design, at the time of the premarket submission, or in postmarket clinical studies:

- Sex- and/or gender-specific differences should be included in the risk analysis of the investigational plan during the design and early enrollment stage for an investigational device exemption study;

- For studies that have already begun enrollment but where enrollment is not adequate with respect to sex and/or gender, the sponsor should discuss its plans with FDA;

- Premarket submissions should include data from such studies in addition to previous studies suggesting there is a clinically meaningful sex- and/or gender-specific difference; and

- In cases where a post-approval study is required, sponsors should include sex- and/or gender-specific data in the interim reports when the evidence shows there may be a difference based on such markers.

Based on any of the above information, the FDA may request that a sponsor revise product labeling to ensure patients and healthcare personnel are appropriately informed, or the FDA may require additional studies in one sex or other genders as warranted.

With respect to in vitro diagnostic devices, the FDA recommends that sponsors include data from both males/men, females/women and other study participants at the cutoff selection and cutoff validation stages.

Further, sensitivity, specificity, and positive and negative predictive values, among other metrics as appropriate, should be evaluated by sex and gender.

This device-specific guidance goes on to explain where such information should be included, e.g., in the labeling, summary, or in a specific part of the submission, and provides example language sponsors can model for describing representative enrollment.

As noted above, the status of this guidance is in flux.

Conclusion

It remains to be seen how the FDA will handle currently ongoing clinical studies involving action plans and currently pending marketing applications including such clinical studies.

The possibility of litigation exists on both sides: The agency may be open to challenges if it denies an application or places an investigational new drug application, for example, on clinical hold on the basis that the study is not well controlled because it lacks a meaningfully representative population.

On the other hand, manufacturers have good reason to include representative patient populations in their clinical studies — from the importance of generating appropriate labeling to guarding against potential product liability suits.

We, along with many in industry, await further direction from the FDA on whether these draft guidance documents will be reissued with revisions or formally withdrawn.

The effect on the FDA's statutory authorities likewise remains to be seen. The comment period on the sex differences draft guidance is open until April 7, though, as noted, this may be extended, and may become a central hub of comments in light of these recent developments.

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[1] FDA, Study of Sex Differences in the Clinical Evaluation of Medical Products: Draft Guidance (January 6, 2025) (last visited January 27, 2025).

[2] FDA, Evaluation of Sex-Specific and Gender-Specific Data in Medical Device Clinical Studies: Draft Guidance (January 7, 2025)(last visited January 27, 2025)(archived version dated January 13, 2025 available at https://web.archive.org/web/20250113205205/https://www.fda.gov/media/184854/download).

[3] Diversity action plans are only required for a subset of clinical trials for devices, drugs, and biological products as set forth in sections 505(z) and 520(g) of the FDCA.

[4] Executive Order 14168, Defending Women From Gender Ideology Extremism and Restoring Biological Truth to the Federal Government (January 20, 2025).

[5] Executive Order 14168; Executive Order 14151, Ending Radical and Wasteful Government DEI Programs and Preferencing (January 20, 2025); and Executive Order 14173, Ending Illegal Discrimination and Restoring Merit-Based Opportunity (January 21, 2025). Other FDA links that appear to have been removed include, e.g., ones to the agency's "Health Equity Forum" podcast and adiscussion paper on health equity in medical device trials.

[6] FDA, CDRH Strategic Priorities and Updates: Discussion Paper on Health Equity in

Medical Device Development.

[7] Doctors for America v. Office of Personnel Management, et al., No. 1:25-cv-00322 (D.D.C. 2025).

[8] Doctors for America, Dkt. #1 at ¶ 17.

[9] P.L. 117-328, ("FDORA"), Secs. 3601-3607 (adding section "524B.Guidance on diversity action plans for clinical studies" to the FD&C Act) ("FDORA").

[10] 21 U.S.C. §§ 355(z)(2), 360j(g)(9)(B).

[11] See Sec. 3602 of FDORA.

[12] Id. at 3602(c).

[13] See 21 U.S.C. §§ 355(z), 360j(g).