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Client Alert

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Finally! FDA Issues Updated Draft Guidance on Diversity Action Plans Mandated by FDORA

On June 28, 2024,[i] the U.S. Food and Drug Administration (FDA) announced in the Federal Register the issuance of a draft guidance entitled "*Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies*."[ii] Diversity Action Plans (DAPs) are mandated under the Food and Drug Omnibus Reform Act of 2022 (FDORA),[iii] which was signed into law on December 29, 2022, and amended the Federal Food, Drug, and Cosmetic Act.[iv] Although FDORA required that FDA issue new draft guidance or update existing draft guidance no later than 12 months after FDORA's enactment, the Agency did not meet this deadline. The now-published updated draft guidance is critical for sponsors who are committing resources and actively designing and planning strategies for the implementation of DAPs for covered clinical studies of drugs, biological products, and medical devices.

In accordance with FDORA, the new draft guidance describes the expected format, content, and manner of submission of DAPs, including the timing and processes for obtaining feedback from FDA prior to submission. Sponsors should promptly ensure that company leadership and the teams developing DAPs for upcoming clinical studies understand that this draft guidance provides new information and replaces the prior draft guidance on non-mandatory diversity plans for clinical trials published on April 14, 2022.[v]

Comments to FDA concerning the new draft guidance must be submitted by September 26, 2024. The later final guidance will become binding on the form and manner of DAP submissions. Final guidance also will trigger the mandatory DAP implementation deadline, to occur six months after finalization.

FDA's updated draft guidance does not modify the scope of clinical studies that are covered by FDORA, nor does it modify the DAP requirement. A clinical study of a drug that will require a DAP is "a clinical investigation of a new drug that is a phase 3 study, as defined in section 312.21(c) of title 21, Code of Federal Regulations (or successor regulations), or, as appropriate, another pivotal study of a new drug (other than bioavailability or bioequivalence studies)." A clinical study of a device that will require a DAP is a clinical investigation of (i) "a device for which submission of an application for an investigational device exemption (IDE) is required," or (ii) a device considered to have an approved IDE application under the abbreviated regulatory requirements.

The requirement for DAP submission will be triggered for covered clinical studies where enrollment begins 180 days or more after the date of FDA's future publication of a final guidance. Based on the sequential timelines specified in FDORA, and assuming FDA adheres to the statutory timeline for finalization of the guidance (FDORA directs FDA to finalize its guidance no later than nine months after closing of the comment period on the draft, i.e., no later than June 26, 2025), submission of DAPs will be required for covered clinical studies for which *enrollment commences* on or after December 23, 2025. The timelines for submission differ for drug and device studies.

- For drug studies, sponsors must submit the DAP no later than the date the sponsor submits the protocol to FDA via the Investigational New Drug application (IND) for a phase 3 study or other pivotal study.
- For device studies that require submission of an IDE application to FDA, sponsors must include the DAP in the IDE. For device studies that do not require an IDE, the DAP must be submitted as part of the marketing application—either premarket notification (510(k)), premarket approval (PMA) application, or request for De Novo classification.

FDA's current interpretations of key considerations and processes for interaction with FDA are highlighted below.

DEADLINES FOR SUBMISSION OF DIVERSITY ACTION PLANS

FDA proposes that DAPs not be submitted for the following clinical studies:

- Studies of drugs for which protocols are submitted to FDA within 180 days after publication of the final guidance, even if enrollment is expected to begin more than 180 days after publication of the final guidance.
- Studies of devices proposed in IDE applications received by FDA within 180 days after publication of the final guidance.
- Studies of devices that do not require an IDE application to be submitted to FDA and that are approved by an institutional review board (IRB) or independent ethics committee within 180 days after publication of the final guidance.

THE PRIMARY FOCUS: RACE, ETHNICITY, SEX, AND AGE

FDA emphasizes that goals for clinical enrollment for specific clinical studies must (not "should") be disaggregated by race, ethnicity, sex (biological sex not gender), and age that are "characteristic of the clinically relevant population" that is intended to use the specific drug or device. FDA appears to imply that the focus should be the population of patients in the United States for whom the drug or device is intended, not a global population, though the Agency skirts this important question in the draft guidance.

FDA recently issued other updated draft guidance addressing the collection of race and ethnicity data in FDA-regulated clinical trials.[vi] The Agency, however, has not issued formal guidance regarding how biological sex should be defined. Its current expectation regarding the definition of "sex" is cited in a footnote.[vii] In addition, FDA advises that sponsors should consider the distribution of each of these characteristics in the intended use population for the product. In addition, the Agency stresses that "[i]n some cases, it may be necessary to increase the proportional enrollment of a certain population in the clinical study to evaluate outcomes of interest or other clinically relevant factors in that group."

CONTENT OF THE DIVERSITY ACTION PLAN

- Enrollment goals. FDA advises that enrollment goals should be informed by the estimated prevalence or incidence of a disease or condition in the U.S. intended population (not the global population) for which the product is being developed. The Agency acknowledges that for some diseases and conditions there may be limited or no data to characterize either the incidence or prevalence in the United States based on demographic characteristics. In the situation where these data are not known for a subset of the population that is the target of the drug or device (e.g., patients with a particular genetic mutation), it may be acceptable to consider incidence or prevalence in a broader category of patients with the particular disease. For some products, such as a preventive vaccine intended for a general use population, it may be acceptable to use U.S. census data. For international studies, FDA emphasizes that enrollment should "account for the need to enroll a population representative of the U.S. population." We believe that this is a critical issue for sponsors: how will you justify that a predominantly international enrollment of subjects is representative of the target U.S. population in terms of race, ethnicity, sex, and age? We agree with FDA's recommendation that sponsors should engage early with the appropriate FDA review division to discuss enrollment goals in an international clinical study—or in a program of multiple clinical studies—to meet expectations for an acceptable DAP.
- Rationale for enrollment goals. In addition to estimates of incidence and prevalence of the disease or condition for which the drug or device is being investigated, FDA advises that the rationale should include an overview of the natural history of the disease or condition and risk factors.
    - Drugs: The rationale should include information that suggests a potential difference in safety and effectiveness in the subgroups, such as differences in pharmacokinetics (PK), pharmacodynamics (PD), and safety "by sex, age, or by genetic variations which may be more prevalent in certain racial and ethnic populations." A more complex expectation, where applicable, is the expectation that the sponsor will provide a description of "population-level or individual characteristics that available data suggest may have an impact on the clinical outcomes[.]" FDA expects that sponsors will cite data sources, such as epidemiologic databases and registries, that support sponsor rationales for enrollment goals.
    - Devices: The rationale should include data about the potential for "differential safety and effectiveness of the device across the clinically relevant populations," including available data regarding "sex, age, or genetic variations, which may be more prevalent in certain racial and ethnic populations that are expected to impact clinical outcomes or susceptibility to adverse events." Where applicable (as with drugs), sponsors are also expected to consider population-level or individual characteristics that may impact clinical outcomes. As an example, FDA references how variations in skin pigmentation may affect the performance of certain devices.

- Planned measures to meet enrollment goals. FDA advises that sponsors should identify specific measures intended to enhance enrollment and address retention of pertinent subgroups. In follow-up to recent public meetings on this issue, the Agency recommends consideration of various strategies, including (1) sustained community engagement, (2) implementing training for "cultural competency" and "proficiency" for clinical investigators and research staff, with a particular focus on avoiding biased and stereotyped communications with participants, (3) providing "language assistance" for both staff and participants with limited English proficiency, (4) reducing the burden of participation, (5) improving access to the clinical study, and (6) using decentralized clinical study designs, where appropriate.
    - Implicit in these recommended measures is the potential challenge for sponsors of both drug and device trials to consider enrollment, treatment, and follow-up of participants in community sites and with research personnel who may not previously have had experience or developed expertise in conducting FDA-regulated clinical investigations.
    - Sponsors should carefully consider protocol design to eliminate unnecessary and burdensome protocol requirements and evaluate study entry criteria to ensure that enrollment "exclusions" and "inclusions" do not create unneeded barriers to meeting DAP goals.
    - FDA explicitly advises that sponsors describe the plan to monitor enrollment goals as well as the measures that will be taken if the study is not on track to meet enrollment goals.

INTERACTIONS WITH FDA

FDA provides explicit guidance on the timing and processes for sponsor interaction with the Agency regarding the sponsor's DAP.

- Drugs: FDA advises that its review and feedback will usually be most efficient if the sponsor submits the DAP when it is seeking feedback on the proposed phase 3 clinical trial or other pivotal trial, typically at the End-of-Phase 2 meeting. The draft guidance provides detailed instructions regarding the process for submission, as well as the expected content and format, of the DAP. FDA emphasizes that to ensure a timely and efficient review the sponsor should clearly describe all required elements of the plan. In addition, the plan should be succinct and, in general, no more than 10 pages long. The status of the DAP, including any discussions and correspondence, should be described in the regulatory history for milestone meetings. FDA advises that IND Annual Reports must include data on the total number of participants enrolled in the study to date, including tabulation by age group, gender (meaning sex), and race, as well as a description of progress toward meeting DAP goals. FDA also briefly describes its expectations for the provision of information about the DAP in a New Drug Application (NDA) or Biologics License Application (BLA).
- Devices: FDA advises that for device studies that require an IDE submission to FDA (i.e., studies of significant risk devices), the DAP must be included in the IDE. For this category of device studies, the sponsor may submit a Pre-Submission to request written feedback or a meeting with FDA regarding the DAP. However, for device studies that require a DAP but do not require submission of an IDE, the draft guidance states that "FDA anticipates than many Diversity Action Plans for studies not requiring submission of an IDE application may be developed without FDA's input." FDA advises that sponsors may request a Pre-Submission if FDA's feedback on "specific questions" is needed to guide product development or submission preparation. The draft guidance provides brief instructions regarding the content and format of information in a submission that includes a DAP,

such as an IDE, marketing application, or Pre-Submission. Because of ambiguity regarding the threshold for requesting feedback on a proposed DAP, we anticipate that the Center for Devices and Radiological Health may receive requests for further clarification about this procedure.

REQUESTING DIVERSITY ACTION PLAN WAIVERS

FDORA provides that FDA may waive the requirement to submit a DAP, or any part thereof, on FDA's initiative or following a sponsor's request if certain criteria are met.[viii] In the draft guidance, FDA emphasizes that full or partial waivers will be granted in "rare instances" and with the following considerations.

- FDA does not generally intend to waive a DAP requirement, even if the disease or condition impacts patients who are relatively homogeneous in terms of race, ethnicity, sex, or age. Sponsors should submit data in support of enrollment goals explaining why the patient population is homogenous.
- Sponsors should submit a request for a waiver "as early as feasible, and no later than 60 days before the Diversity Action Plan is required for submission." FDA cautions that a waiver request should be submitted early enough that, if it is denied, the sponsor has sufficient time to prepare and submit a DAP.
- If multiple clinical studies are planned to support phase 3 or pivotal drug studies, sponsors should not seek a waiver for each study. Instead, sponsors should specify how DAP enrollment goals will be met across the clinical study program and provide DAP enrollment goals for specific studies.
- FDA provides instructions regarding how a waiver request should be submitted for clinical studies of drugs and devices.

PUBLIC POSTING OF KEY INFORMATION FROM DIVERSITY ACTION PLANS

FDORA does not mandate that sponsors publicly disclose information about the enrollment goals of a DAP or the rationale for such goals. In the draft guidance, FDA recommends that sponsors consider public posting of DAP information on their website for individual clinical studies, "namely their clinical enrollment goals disaggregated by race, ethnicity, sex, and age group, and a brief description of the measures taken to achieve the stated goals." We note that the ClinicalTrials.gov website has not yet developed a specific platform for entry of these data with linkage to a clinical trial. FDORA also does not mandate that this information be disclosed to potential clinical subjects in the consent document. IRBs, however, may require consent forms to include additional disclosures beyond those specified at 21 C.F.R. Part 50. Drug and device companies should consider the potential benefits and risks of publicly disclosing and updating information about their DAPs.

SUMMARY

In this new draft guidance, FDA addresses its current expectations regarding the content and format of DAPs, as well as its expectations regarding sponsor rationales for enrollment goals, plans for monitoring whether enrollment goals are being achieved, and steps that will be taken to modify DAPs if goals are not being achieved. Company leadership and teams developing DAPs for upcoming drug and device clinical studies should promptly assess whether current draft DAPs are aligned with the recommendations in this new draft guidance. Although DAPs can identify multiple demographic variables, companies should ensure that there is laser focus on enrollment goals specific to the target patients who are expected to use a drug or device, and that enrollment goals are disaggregated for the "big four" demographic categories: race, ethnicity, sex (not gender), and age. Companies should also be aware that FDA has signaled that the granting of waivers, or partial waivers, will be rare.

If you have questions regarding the new draft guidance, would like assistance in preparing comments, or would like to discuss potential risks and benefits of specific diversity goals or approaches, we are glad to help. Please contact Beverly Lorell, Chris Markus, Kyle Sampson, or Elaine Tseng for more information.

[i] FDA, Notice of availability, *Diversity Action Plans To Improve Enrollment of Participants From Underrepresented Populations in Clinical Studies; Draft Guidance for Industry*, 89 Fed. Reg. 54,010 (June 28, 2024), https://www.govinfo.gov/content/pkg/FR-2024-06-28/pdf/2024-14284.pdf.

[ii] FDA, Draft Guidance for Industry, *Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies* (June 2024) [hereinafter "*2024 DAP Draft Guidance*"], https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-action-plans-improve-enrollment-participants-underrepresented-populations-clinical-studies.

[iii] Consolidated Appropriations Act, Pub. L. 117-328, §§ 3601-3603 (Dec. 29, 2022).

[iv] Sections 505(z)(2) and 520(g)(9)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. §§ 355(z)(2) & 360j(g)(9)(B).

[v] *See* FDA, Notice of availability, *Diversity Plans To Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry*, 87 Fed. Reg. 22,211 (April 14, 2022).

[vi] FDA, Draft Guidance for Industry, *Collection of Race and Ethnicity Data in Clinical Trials and FDA-Regulated Medical Products* (Jan. 2024), https://www.fda.gov/media/175746/download.

[vii] In the draft guidance, FDA states:

> For the purposes of this guidance, "sex" is a biological construct based on anatomical, physiological, hormonal, and genetic (chromosomal) traits, and is generally assigned based on anatomy at birth typically categorized as male or female, but variations occur. Variations of sex refers to differences in sex development or intersex traits. See *Measuring Sex, Gender Identity, and Sexual Orientation* (2022). National Academies of Science, Engineering, and Medicine. Washington, DC: The National Academies Press.

2024 DAP Draft Guidance § I n.5.