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Updated FDA Draft Guidance Instructs Sponsors on Content, Format, Timing, and Procedures for Submitting Diversity Action Plans for Clinical Studies

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Back in 2022, we wrote about U.S. Food and Drug Administration's (FDA) draft guidance, "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials." On June 24, FDA replaced that draft guidance with a new one, titled "Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies" (Draft Guidance).[1] The Draft Guidance, which tracks new requirements under the Food and Drug Omnibus Reform Act (FDORA),[2] provides more detail on the applicability, elements, and timing of diversity action plans (DAPs) and expands their scope to cover age and sex in addition to race and ethnicity.[3] FDA also recognizes that other factors such as geographic location, gender identity, sexual orientation, socioeconomic status, physical and mental disabilities, pregnancy status, lactation status, and co-morbidities are relevant and should be considered by sponsors when developing DAPs.[4] These changes help achieve the intent of DAPs to increase enrollment of historically underrepresented populations in clinical studies to help improve the applicability and generalizability of study results for the intended use population.[5] Importantly, because FDORA specifically charges FDA with issuing guidance on DAPs,[6] much of the new Draft Guidance — unlike most other FDA guidance documents, including the 2022 draft guidance — will be binding once finalized.

This article discusses the new recommendations and requirements in the Draft Guidance and what sponsors can expect when developing DAPs, including:

- When DAPs are required;
- Content and format requirements for DAPs;
- Timelines and procedures for submitting DAPs;
- Criteria for requesting DAP waivers; and
- Key takeaways for sponsors.

When Are Diversity Action Plans Required?

FDORA specifies which trials will require DAPS; the Draft Guidance expands on and clarifies these requirements.

For drugs, DAPs are required for Phase 3 trials and other pivotal clinical trials.[7] For devices, DAPs are required for (1) all clinical trials subject to an Investigational Device Exemption (IDE), and (2) trials not subject to an IDE that, as clarified in the Draft Guidance, are "designed to collect definitive evidence of the safety and effectiveness of a device for a specified intended use."[8] (Certain IDE-exempt devices will never require DAPs.)[9] While FDORA specifies that DAPs will be required only for studies for which enrollment begins after 180 days from publication of the final guidance,[10] recognizing that sponsors may begin study activities before commencing enrollment, FDA explains in the Draft Guidance that it will not expect DAPs for the following additional studies:

- Drug studies for which enrollment is scheduled to begin after 180 days from the publication of the final guidance, but for which the protocols are submitted within 180 days of the publication of the final guidance;
- Clinical studies of devices submitted in an IDE application within 180 days from the publication of the final guidance; and
- Clinical studies of devices that do not require an IDE application that are approved by Institutional Review Board (IRB) or Independent Ethics Committee (IEC) within 180 days from the publication of the final guidance.[11]

Content and Format Requirements for Diversity Action Plans

The 2022 draft guidance included five elements; the new Draft Guidance repackages these into three elements to track the explicit requirements of FDORA: (1) enrollment goals; (2) rationale for enrollment goals; and (3) measures to meet enrollment goals.

The "enrollment goals" section of a DAP must include goals disaggregated by race, ethnicity, sex, and age of the clinically relevant study population. Enrollment goals should be tied to the estimated prevalence or incidence in the U.S. of the disease or condition for which the medical product is being studied. However, where increased enrollment of certain populations may be warranted to detect clinically important differences in a subset of the study population, FDA will require sponsors to provide a rationale for deviating from the estimated prevalence or incidence of the disease or condition in the U.S. in setting their enrollment goals. When the estimated prevalence or incidence of the disease or condition by demographics in the U.S. population is not available, sponsors may consider using prevalence and incidence information for the broader disease or the general U.S. population demographics in setting enrollment goals. Additionally, the Draft Guidance provides further recommendations on developing DAPs for rare diseases, multiple studies, and global studies. It also provides recommendations on using appropriate real-world evidence sources to gather prevalence and incidence information for a disease or condition.[12]

The "rationale" section of a DAP must include background information on the history of the disease, its risk factors, prevalence, and incidence estimates, among other information. Additionally, for drugs, FDA recommends sponsors include available pharmacokinetics and pharmacodynamics data relating to differential safety and effectiveness and population-level or individual characteristics that may impact clinical outcomes. For devices, sponsors should include similar information related to device performance (*e.g.*, variations in skin pigmentation can affect performance of certain devices).[13]

The “measures to meet enrollment goals” section should focus on specific steps to ensure adequate representation of the clinically relevant population for a specific clinical study. To meet this requirement, FDA encourages sponsors to consult with patients and health care providers to identify enrollment and retention barriers during the development of DAPs. Some examples of enrollment and retention strategies include implementing sustained community engagement, providing cultural competency and proficiency training for clinical investigators and research staff, educating participants on the clinical study, employing strategies to reduce participant burden, improving access to the clinical study, and employing clinical study decentralization strategies whenever possible. Sponsors should describe plans to monitor enrollment goals so that the sponsors can identify and address barriers promptly to meet their goals.[14]

Timelines and Procedures for Submitting Diversity Action Plans

For drugs, FDA encourages sponsors to submit DAPs to the relevant Investigational New Drug (IND) application as soon as practicable. FDA recommends sponsors submit DAPs when seeking feedback on a clinical study (typically End-Of-Phase 2 meeting) to drive efficiency. But sponsors must submit DAPs no later than the date on which the sponsors submit the protocol for a Phase 3 study or other pivotal study.[15]

For devices, sponsors must submit DAPs with the IDE application. For studies that do not require an IDE, sponsors must submit DAPs as part of the device’s premarket notification (510k), premarket approval (PMA) application, or De Novo classification request. FDA expects that there will be studies for certain devices for which DAPs will not be required and encourages sponsors to reach out to FDA via the Q-submission process with questions.[16]

Diversity Action Plan Waivers

Pursuant to FDORA,[17] the Draft Guidance specifies the circumstances under which sponsors may obtain waivers for DAPs — both with respect to DAPs in their entirety or for certain elements. FDA anticipates that submission of a DAP will be possible in most cases; for example, even if the clinically relevant study population is homogenous, FDA would still require a DAP but would expect the “rationale” section to explain a study’s otherwise less expansive enrollment goals. Thus, given the importance of increasing enrollment of historically underrepresented populations in clinical research, FDA will grant waivers only in rare circumstances. FDA will determine the appropriateness of waivers on a case-by-case basis based on the following statutory criteria: (1) a waiver is necessary considering what is known or what can be determined about the disease incidence or prevalence in the U.S. for which the new medical product is being developed; (2) it is impracticable to conduct a clinical study in accordance with a DAP; and (3) a waiver is necessary for public emergency reasons. In terms of timelines, sponsors should submit waiver requests as soon as practicable but no later than 60 days submission of a DAP is required.[18]

Key Takeaways for Sponsors

In our article on the 2022 draft guidance, we provided some takeaways for sponsors including informed consent, anti-kickback, and post-marketing considerations. Because the new Draft Guidance essentially repackages the DAP elements from its 2022 predecessor to track FDORA, those considerations remain relevant. Thus, sponsors should follow existing FDA guidance to ensure compensation of clinical trial participants does not constitute undue

influence,[19] and any compensation should be in line with the Office of Inspector General (OIG) advisory opinions in which OIG has elected not to pursue sanctions because of the importance of ensuring diverse clinical trial enrollment.[20]

However, the new Draft Guidance is much more detailed, provides a comprehensive list of requirements for sponsors, and, as noted above, when the Draft Guidance is finalized, its requirements will be binding. Accordingly, the new Draft Guidance yields additional takeaways for sponsors.

First, context will matter. The Draft Guidance explains that if several studies for the same medical product require a DAP under FDORA, the sponsor should (but is not required to) also develop and implement a comprehensive diversity strategy across the entire clinical development program, including in early studies.[21] Similarly, DAPs for globally conducted clinical trials should describe participant enrollment goals for the entire study while also accounting for the need to enroll a population representative of the U.S.[22] And, as discussed above, FDA's expectations for the enrollment goals in a DAP and the means to achieve them will vary based on the clinically relevant study population, the size of the study, and other factors — *e.g.*, in trials for rare diseases.

Second, although the Draft Guidance is not yet finalized, and will likely remain unfinalized for some time, sponsors may be best served to begin efforts now to comply with the Draft Guidance as soon as possible. Not only may preparing a comprehensive DAP be time and resource-intensive, but the Draft Guidance — even if unfinalized — represents FDA's current thinking on DAPs. Thus, complying with the terms of the Draft Guidance now maximizes a sponsor's chances for seamless progression through the development and application/notice process.

Finally, while the 2022 draft guidance may have been more susceptible to judicial challenges now that the Supreme Court has overturned *Chevron*, much of the new Draft Guidance tracks the express requirements of FDORA. To be sure, some of the Draft Guidance's specifics as to enrollment goals and the means of achieving them are not expressly prescribed by the statute, but FDORA provides support for many of the requirements of the Draft Guidance.

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[1] FDA, Draft Guidance for Industry, "Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies" (June 2024), *available at* https://www.fda.gov/media/179593/download.

[2] *See* Section 3601 of the Food and Drug Omnibus Reform Act of 2022, Consolidated Appropriations Act, 2023, Pub. L. No. 117-328, 136 Stat. 4559 (Dec. 29, 2022), *available at* https://www.congress.gov/117/plaws/publ328/PLAW-117publ328.pdf.

[3] *See* Draft Guidance at 1-2.

[4] *Id.* at 5.

[5] *Id.* at 1.

[6] *See* 21 U.S.C. § 355(z)(3).

[7] *Id.* § 355(z)(1).

[8] *Id.* § 360j(g)(9); Draft Guidance at 6-7.

[9] 21 U.S.C. § 360j(g)(9)(A) (citing the IDE exemptions at 21 C.F.R. § 812.2(c))

[10] *See* Food and Drug Omnibus Reform Act of 2022 (FDORA) § 3602(c), included as part of the Consolidated Appropriations Act (December 2022) (P.L. 117-328).

[11] Draft Guidance at 2.

[12] *Id.* at 8-11.

[13] *Id.* at 12-13.

[14] *Id.* at 13-14.

[15] *Id.* at 14-15.

[16] *See id.* at 15.

[17] *See* 21 U.S.C. § 355(z)(4).

[18] Draft Guidance at 19-20.

[19] *See* FDA, Guidance for IRBs, Clinical Investigators, and Sponsors, *Informed Consent* at 8, 13-14 (Aug. 2023), *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent.

[20] *See, e.g.*, OIG Adv. Op. No. 22-05 at 7 (Mar. 16, 2022) ("[T]he cost-sharing subsidies that would be offered under the Proposed Arrangement appear to be a reasonable means to facilitate enrollment of a socioeconomically diverse set of subjects by removing a potential financial barrier to participation in the Study."); OIG Adv. Op. No. 21-13 at 7 (Oct. 4, 2021) ("The coinsurance subsidies offered under the Proposed Arrangement appear to be a reasonable means to facilitate enrollment of a diverse set of subjects by removing a potential financial barrier to participation in the study.").

[21] Draft Guidance at 7.

[22] *Id.* at 10.

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