

Analyzing FDA Draft Guidance On Clinical Trial Diversity

By **Linda Malek, Jason Johnson and Stephen Holland** (July 19, 2024, 4:35 PM EDT)

On June 26, the U.S. Food and Drug Administration released draft guidance on clinical trial diversity action plans, outlining new required elements of drug and device submissions, updating recommendations for sponsors, and setting in motion the timeline for potential enforcement from the FDA.

The long-awaited guidance represents a key step forward for efforts to diversify enrollment in clinical trials, and will improve understanding at the FDA and in the research community about the accuracy and reliability of products across a more representative population, as well as access to innovative therapies and clinical trials for those long underrepresented in clinical research.

These goals were at the heart of Congress' intent in enacting new requirements for drug and medical device sponsors under the Food and Drug Omnibus Reform Act, or FDORA.

In this article, we analyze the new guidance and provide important considerations for sponsors and clinical researchers.

Background

Under FDORA, drug and device sponsors are required to submit diversity action plans ahead of pivotal clinical studies.

The statute requires action plans to include (1) the sponsor's goals for enrollment in their clinical trial, (2) the sponsor's rationale for those goals, and (3) an explanation of how the sponsor intends to meet those goals.

Complying with the requirements of the statute and following the recommendations in the guidance will require sponsors to incorporate considerations of diversity early and throughout the clinical trial planning and development process.

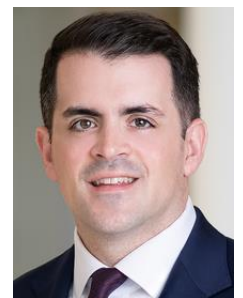
Much of the information in the draft guidance document is subject to the FDA's general disclaimer that guidance merely reflects the agency's thinking, and should only be viewed as recommendations unless specific regulations or statutes are cited. However, the agency noted that FDORA requires the FDA to specify the form and manner for the submission of diversity action plans in guidance, and guidance on



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these issues should be considered binding requirements once this guidance is finalized.

The FDA's guidance, and this article, differentiate what is "required" by FDORA, and what sponsors "should" do pursuant to recommendations.

Failure to comply with the guidance document's form and manner requirements, or the diversity action plan statutory requirements otherwise included in FDORA, may lead to a delay in the medical product review process or enforcement action from the FDA.

Key Elements of Diversity Action Plans

Enrollment Goals

Sponsors are required under FDORA to specify their enrollment goals in diversity action plans, disaggregated by age group, sex, and racial and ethnic demographic characteristics of clinically relevant study populations.

Additionally, while not required by FDORA, the FDA encourages sponsors in the guidance to consider additional factors when developing enrollment goals, including geographic location, gender identity, sexual orientation, socioeconomic status, physical and mental disabilities, pregnancy status, lactation status, and comorbidity.

Enrollment goals should be informed by an estimated prevalence of the disease or condition in the U.S. for which the drug or device is being investigated and the intended population for the product.

Recognizing that multiple studies are often used in clinical development of a drug or device, the FDA noted that the diversity action plans for each study should all reflect a strategy that adds up to an overall proportionate representation, but each individual study did not necessarily need to include proportionate representation.

For studies conducted in other countries in addition to the U.S., diversity of the entire trial population should be considered in the diversity action plan and not just the U.S. population of the trial.

Rationale

FDORA requires diversity action plans to include sponsors' rationale for setting its enrollment goals.

In the draft guidance, the FDA recommends that the rationale should include background information for the disease or condition for which the medical product is being investigated, including prevalence and incidence estimates, based on the best available data.

The FDA also recommends that sponsors include considerations about whether there is a potential difference in safety or efficacy in the product for certain groups, such as different age groups, sexes, or among genetic variations that may be more prevalent in certain racial and ethnic populations in their rationale.

Measures to Meet Enrollment Goals

Diversity action plans are required to include an explanation of a sponsor's plans on how it intends to

meet its enrollment goals. In the guidance, the FDA said that while broad strategies to address systemic barriers in clinical trial participation rates are important, the agency expects sponsors to focus on specific measures they plan to take for the clinical trial at hand. These may include:

- Cultural competency training for investigators and research staff;
- Language assistants for clinical trial participants with limited English proficiency;
- Reducing participant burden by paying for transportation costs and providing dependent care;
- Limiting clinical trial study exclusion criteria;
- Selecting clinical study site locations that serve demographically diverse populations; and
- Employing decentralized clinical trials, a topic on which the FDA has recently published additional draft guidance.

The diversity action plan should also include a description of the sponsor's plan to monitor enrollment goals, and recommends that sponsors include the measures sponsors may take if, upon beginning enrollment, it appears that enrollment goals may not be met.

When to Submit Diversity Action Plans

The statutory requirement to submit diversity action plans goes into effect 180 days after the draft guidance is finalized, if enrollment in the study will begin 180 days or more after the final guidance is published.

The FDA — recognizing that planning and study activities begin before enrollment commences — said in its guidance that the agency does not expect a diversity action plan to be submitted for the following:

- Clinical trials for drugs with protocols that are submitted within 180 days after the publication of the final guidance, and enrollment is scheduled to begin 180 days after the publication of the final guidance;
- Clinical trials of devices received by the FDA in investigational device exemption, or IDE, applications within 180 days after publication of final guidance; and
- Clinical trials for devices that do not require an IDE application to be submitted, that are approved by an institutional review board or independent ethics committee within 180 days after publication of the final guidance.

After the requirements go into effect for other clinical trials, drug sponsors will be required to submit diversity action plans "as soon as practicable, but no later than the date on which the sponsor submits the protocol to FDA for the phase 3 study, or, as appropriate, another pivotal study."

Device sponsors will be required to submit diversity action plans in IDE applications where such applications are necessary. Where such applications are not necessary, diversity action plans must be submitted as part of the device's premarket notification (510(k)), premarket approval application, or de novo classification request.

While these deadline requirements are set in law, the FDA strongly recommends that sponsors develop and implement a comprehensive diversity strategy that stretches across the entire clinical development program, including in earlier studies. The agency also encourages sponsors to discuss diversity action plans with review divisions early in the development process.

Additional Formatting and Submission Recommendations and Requirements

In submitting diversity action plans, the FDA recommends that sponsors describe required information succinctly, generally not exceeding 10 pages, excluding references, and with limited cross-referencing to previously submitted documents.

The submission should include a cover letter that indicates whether the submission is a new or revised diversity action plan, with "DIVERSITY ACTION PLAN-Initial" or "DIVERSITY ACTION PLAN-Revised" written in large, bold type.

The title page of the submission should include all relevant administrative information, including:

- The name of the medical product;
- The IND/IDE number, if applicable (for drugs, the diversity action plan is required to be submitted to the IND, and for significant risk medical devices, the plan is required to be submitted to the IDE) and/or other relevant submission information (for example, information necessary to identify previous Q-submissions or marketing submissions for the medical device);
- The proposed indication or indication(s) for use statement and the intended use;
- Clinical study identification information, e.g., the NCT number, title, and study ID; and
- The version number of the diversity action plan and the date.

The FDA noted in the guidance that existing regulations require IND sponsors to submit annual reports that include for each study the total number of subjects enrolled broken down by age group, gender and race.

The FDA now recommends that for these annual reports, sponsors should include an update related to progress made toward the diversity action plan enrollment goals. If goals are not on track for being met at the conclusion of the study, the FDA recommends that the annual report should include the reasons why the sponsor is not meeting or does not expect to meet the enrollment goals, and the sponsor's plan for mitigating a failure to meet enrollment goals.

Additionally, the FDA recommends that sponsors include a brief overview of diversity action plans in marketing submissions, including an assessment of whether enrollment goals were met, and as appropriate, an explanation of what measures may have contributed to the observed outcomes with respect to enrollment goals.

Additionally, sponsors are reminded that existing requirements for including safety and effectiveness data tabulated by race, gender, and age in new drug applications remains in effect, in addition to the new requirements laid out in FDORA and in this guidance.

Agency Feedback and Plan Modifications

For drugs, the FDA may or may not provide feedback on a diversity action plan on its own initiative, depending on the specifics for each clinical development program.

Sponsors may request feedback on diversity action plan submissions and may include questions related to diversity action plans in meeting discussion topics with the FDA. Sponsors may also modify diversity action plans based on the feedback they receive, or for any other reason. In submitting a modification, sponsors must also include a summary of those modifications and a rationale for making changes.

For devices, sponsors may submit a presubmission request for written feedback or a meeting with the FDA to discuss a diversity action plan. Where an IDE is not required — i.e., a device to be marketed under 510(k), a premarket approval application, or de novo classification — the FDA encourages sponsors to seek feedback when appropriate, including when the agency's feedback on questions is necessary for product development.

However, the FDA noted in the draft guidance that a presubmission is not required for non-IDE products, and sponsors may move forward without seeking FDA input. Device sponsors may also submit modifications to diversity action plans, but are similarly required to summarize and justify those modifications in resubmitting the plan.

Waivers

FDORA allows the FDA to waive diversity action plan requirements on its own or upon request from a sponsor if the agency determines that such waiver is necessary based on:

- What is known about the prevalence or incidence of the disease;
- If conducting a trial under a diversity action plan would be impracticable; or
- If a waiver is necessary to protect public health during a public health emergency.

The statute ultimately gives the FDA discretion as to when waivers may be granted, and the draft guidance makes clear that the agency will only issue waivers "in rare instances" based on a case-specific determination.

The draft guidance specifically notes that the FDA will generally not waive diversity action plan requirements even if the disease or condition under study is relatively homogenous with respect to race, ethnicity, sex or age group — i.e., a disease or condition that generally only affects one sex or children of a certain age.

In those instances, the FDA still expects sponsors to submit a plan, but sponsors should explain those circumstances in the plan's rationale section. If a sponsor plans to submit a request for a waiver, it should be done early, as the agency may take up to 60 days to consider a waiver request.

Takeaways for Sponsors

To prevent delay in a drug or device application, sponsors should consider diversity in clinical trial enrollment early and throughout the development process, and engage compliance professionals to

ensure diversity action plan submissions adhere to the FDA recommendations and meet all legal requirements, including those specified as requirements in this guidance.

Sponsors should likewise incorporate clinical trial sites early in diversity planning conversations.

Those wishing to submit comments on the draft guidance must do no later than Sept. 26. FDORA requires the FDA to finalize the guidance no later than nine months after closing the comment period, and requirements for sponsors will begin to go into effect 180 days thereafter.

Stakeholders should monitor and plan to adhere to this timeline, while recognizing that these deadlines can and frequently do slip — in fact, the draft guidance was released nearly six months after FDORA's statutory deadline.

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