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Client Alert

August 24, 2023

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FDA Issues Draft Guidance for Obtaining Postmarket Data on Underrepresented Populations in Drug Clinical Trials

The Food and Drug Administration (FDA) has issued new draft guidance, *Postmarketing Approaches to Obtain Data on Populations Underrepresented in Clinical Trials for Drugs and Biological Products*[1] (the *Draft Postmarketing Approaches Guidance*), that provides the Agency's current thinking on requirements and considerations for obtaining safety and effectiveness information on drugs and biological products in the postmarketing setting in "historically under-represented patient populations" in clinical trials when such information has not been able to be collected premarket.

Applicants of New Drug Applications (NDAs) are required to present integrated summaries of effectiveness data by gender, age, and racial subgroups, and to identify any dose or dose interval modification needed for specific subgroups (21 C.F.R. 314.50(d)(v)). Applicants also are required to present integrated summaries of safety data by gender, age, and racial subgroups (21 C.F.R. 314.50(d)(vi)). Beginning 180 days after FDA finalizes guidance on the subject (the latter likely by the end of 2024), applicants will be required to submit Diversity Action Plans for each phase 3 clinical study or other pivotal study of a drug.[2] The Agency strongly recommends that data from representative patient populations be collected premarket to support these requirements—and in fact "early in drug development" to inform clinical trials. But FDA recognizes that, in some instances (for example, areas of unmet medical need), such information may not be able to be obtained prior to marketing.

The *Draft Postmarketing Approaches Guidance* may signal FDA's intent to require postmarket collection of data about one or more subpopulations (e.g., those related to age, biologic sex, race, ethnicity, geographic location, and socioeconomic status) if initial Diversity Action Plans yield inadequate data in the premarket context. The *Draft Postmarketing Approaches Guidance* also clarifies that, for drugs approved under accelerated approval, patient populations in postmarket confirmatory trials are expected to represent the diversity of patients who will use the drug. Finally, the draft guidance shares FDA's thinking with respect to design and statistical considerations of the subpopulation analyses.

FDA'S TOOLS (POSTMARKETING REQUIREMENTS AND POSTMARKETING COMMITMENTS)

The draft guidance outlines FDA's authorities to impose postmarketing requirements (PMRs) and postmarketing commitments (PMCs) to address insufficient safety data regarding a patient subpopulation.[3] In order to require a postmarketing clinical trial in particular, FDA must first find (1) that adverse event surveillance and the active risk identification and analysis (ARIA) system will be insufficient to assess a known serious risk, signals of a serious risk, or an unexpected serious risk in a patient subpopulation that is expected to be exposed to the drug; and (2) that clinical studies other than a clinical trial equally will be insufficient. If these conditions are met, FDA may require a clinical trial or trials to assess or identify a serious risk in a subpopulation, potentially including reduced effectiveness under the conditions of use prescribed in labeling.

- As example, FDA cites a potential PMR for an applicant to assess incidence rates of specific adverse events in subpopulations defined by race, ethnicity, sex, or age compared to overall populations when "there are data to suggest that those adverse events may occur at a higher rate in these populations but an insufficient number of participants from these populations participated in the pivotal trial to adequately evaluate the signal."[4]
- FDA also provides the example of issuing a PMR "if there is data to suggest a signal of a serious risk related to reduced effectiveness in an underrepresented population or a subgroup of patients with a particular genetic mutation that occurs more commonly in patients of a particular race."[5]

FDA emphasizes that it may also enter into a written agreement with an applicant to conduct postmarketing clinical studies through a PMC, including clinical trials, other clinical studies, or additional sources, if it deems that there is insufficient safety or efficacy data for a subpopulation, such as a group defined by race, ethnicity, sex, or age.

Notably, the *Draft Postmarketing Approaches Guidance* provides no clarity regarding the criteria FDA may use to determine that there is "insufficient" data for a subgroup—we expect this to be a focus of stakeholder comments.

DESIGN AND STATISTICAL CONSIDERATIONS FOR POSTMARKETING STUDIES OF SUBPOPULATIONS

The *Draft Postmarketing Approaches Guidance* provides a grab bag of suggestions for the design of postmarketing clinical studies to address deficiencies in safety or efficacy data for patient subpopulations.

- For single-arm trials, FDA proposes studies in a subpopulation designed with use of (1) a sample size to "rule out" an historical problematic rate of safety or efficacy of the drug, (2) a Bayesian posterior probability model to exclude the historical rate at pre-specified levels, and (3) the inclusion of pharmacokinetic (PK) and pharmacodynamic (PD) data (if applicable). For a premarket clinical trial, FDA proposes enrollment and analysis of underrepresented subpopulations as a separate cohort such that the separate cohort may remain open and collect more data after enrollment of the primary analysis population is closed.
- For randomized trials planned or ongoing at the time of an NDA or Biologics License Application (BLA) submission, FDA proposes the use of "enrichment strategies" to obtain additional postmarket data in subpopulation(s) of interest or stratification based on subpopulation(s) of interest, as well as the collection of PK and PD data (if applicable). The draft guidance fails to provide any insight regarding the conundrum of powering such analyses to determine if any result regarding an adverse safety or efficacy signal is or is not the play of chance.
- Regarding use of real-world data (RWD), FDA cautions that there are "multiple complex issues" regarding its use to obtain information on traditionally underrepresented populations.

- For the use of pooled data across trials or meta-analyses of randomized trials, FDA advises discussion with the relevant review division regarding whether the analyses will be considered adequate.

ADDITIONAL CONSIDERATIONS

The draft guidance stresses the importance of a sponsor discussing its approach to address underrepresented patient subpopulations with the FDA review division early in the product development program. It advises consideration of the guidance for industry *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials*[6] and reaching agreement with FDA of "appropriate benchmarks for an inclusive and representative data package that is specific to each development plan." FDA cautions that a marketing application comprised of patients predominantly outside of the United States may trigger requirements or requests for additional clinical studies to characterize the safety or efficacy of a drug in relevant patient subpopulations in the United States.

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We recommend that companies begin familiarizing themselves now with the new legal requirements related to Diversity Action Plans and how those requirements will impact clinical trial designs and drug development programs—including the possibility of postmarketing studies to obtain data on underrepresented populations.

FDA is requesting comments on the draft guidance by October 10, 2023. Please let us know if you have any questions or concerns regarding this draft guidance, or if we can assist you with developing your comments.

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[1] *See* https://www.fda.gov/media/170899/download.
[2] Section 505(z) of the FD&C Act, as added by section 3601 of The Consolidated Appropriations Act, 2023 (enacted December 29, 2022).
[3] *See, e.g.*, section 505(o)(3) and 506 of the FD&C Act (regarding postmarketing requirements); section 506B of the FD&C Act, 21 CFR 314.81, 601.70 (regarding postmarketing commitments).
[4] *Draft Postmarketing Approaches Guidance,* at 4.
[5] *Id*. at 5.
[6] *See* https://www.fda.gov/media/157635/download.