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FDA Issues Draft Guidance on Diversity and Inclusion in Clinical Trials

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With its disproportionately greater impact on minority populations in the United States, the COVID-19 pandemic has illuminated longstanding health inequities in the United States, and increased attention on the importance of including racial and ethnic minorities in clinical trials for vaccines and other medications. The U.S. Food and Drug Administration (FDA or "Agency") has taken a leading role in promoting greater diversity and inclusion in clinical trials, most recently in its April 2022 draft guidance, *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry*; *Availability* ("2022 Draft Guidance").[1]

Race and Ethnicity Matter in Drug Development

Race and ethnicity can serve as surrogates for biological differences in drug response. For instance, race-based differences in the metabolism and disposition of some drugs due to genetic variations have been identified.[2] These differences can require alterations in drug dosing to achieve the desired result. As an example, interpatient variability has been observed across ethnicities when optimizing maintenance dosing of the anticoagulant medication warfarin.[3] This variability is believed to be due to genetic variations that affect the enzyme responsible for warfarin's metabolism. The potential for racial and ethnic contributions to drug action should be a consideration in the drug development process.

The makeup of clinical trial participants remains biased for the White population, even though the White (alone) population comprises just 60% of the population in the U.S.[4] In February 2021, the FDA published a report reviewing the demographics of clinical trial participants involved in 53 drug approvals in 2020, and found that 75% of the 32,000 patients enrolled were White, whereas 8% were Black or African American, 6% were Asian, and 11% were Hispanic.[5] The FDA's report highlights the level of disproportion in the demographics of clinical trial participants as compared to the demographics of the U.S. population. To the extent that the disproportional demographics of clinical trial participants diminish the confidence in those trials by underrepresented populations, the disproportionality also contributes to the health care disparities of underserved populations.

The scientific community and U.S. Congress have been addressing the issue of racial and ethnic disparities in clinical trials for decades. The National Institutes of Health (NIH) Revitalization Act of 1993 established guidelines for the inclusion of women and minorities in clinical research and required a valid analysis of whether the variables being studied affect women or members of minority groups differently than other trial participants.[6] The 21st Century Cures Act, signed into law on December 13, 2016, also requires the NIH director to include women and minorities in NIH-funded clinical research in addition to requiring a valid analysis of the variables.[7] As discussed below, in recent years, the FDA has endeavored to increase participation of underrepresented populations in clinical trials, most recently with its latest 2022 Draft Guidance.

FDA's Prior Efforts to Address Diversity in Clinical Trials

The last decade in particular has seen the FDA strengthen its efforts to promote diversity in clinical trials. Pursuant to the Food and Drug Administration Safety and Innovation Act of 2012, the FDA was directed to provide a report to the U.S. Congress concerning the inclusion and analysis of demographic subgroups in applications for drugs, biologics and devices, including analysis of race and ethnicity, among other categories.[8] The FDA reviewed its policies and regulations and issued its report in 2014 outlining an action plan to encourage greater clinical trial participation, including collaborating with industry, other federal agencies and interested stakeholders to improve clinical trial diversity.[9] This resulted in the FDA analyzing and reporting on the diversity of participants in clinical trials as part of its *Drug Trials Snapshot* program,[10] established in 2015 to increase the visibility of clinical trial enrollment by race, ethnicity, age and gender. In an effort to maintain transparency, the FDA has been publishing information about patient representation in clinical trials for drugs and biologics within a month of the approval date.[11]

In 2016, the FDA issued its guidance on the *Collection of Race and Ethnicity Data in Clinical Trials* ("2016 Guidance").[12] The 2016 Guidance recommended that sponsors collect and report the demographics for clinically relevant populations with regard to age, gender, race and ethnicity. It also recommended that sponsors submit a plan to the FDA at the earliest phase of development to address inclusion of clinically relevant subpopulations for drugs, biologics and medical devices for discussion with the Agency no later than the end of the clinical Phase 2 meeting.[13] The guidance stopped short, however, of recommending an actual level of inclusion of racial and ethnic groups in clinical trials, or that clinical trial demographics precisely mirror the U.S. population.

More recently, in November 2020, the FDA issued another diversity-focused guidance, *Enhancing the Diversity of Clinical Trial Populations - Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry* ("2020 Guidance").[14] The FDA's 2020 Guidance promotes diversity in clinical trials by making recommendations to help broaden eligibility criteria and improve clinical trial recruitment, again to better represent and reflect the population most likely to use the drug. Specifically, the FDA's 2020 Guidance proactively recommended approaches that sponsors should consider during trial design using methodologies that will facilitate enrollment of a broader population. For example, using an adaptive clinical trial design would allow for pre-specified trial design changes during the trial when data become available, and could include altering the trial population. Trial design enrichment was also recommended as a strategy to include targeted populations.[15] This could be a useful trial modification for inclusion/exclusion criteria when a racial or ethnic group has been identified to have a particular severity of a disease, subset of a disease or a disease-associated genetic marker.

The 2020 Guidance also recommended exploring other trial design and conduct considerations to make participation less burdensome for underserved populations with the use of digital health

technologies to increase enrollment and retention by reducing the frequency of visits to a centralized clinical trial facility and reducing financial costs (e.g., reducing travel to clinical sites; lessening the need for dependent care). The 2020 Guidance recommended better communication and education of potential participants of racial and ethnic minorities using different languages to accomplish the goals of increasing participation of underrepresented populations and reducing mistrust of clinical research among certain populations. The 2020 Guidance signaled to sponsors that the FDA would consider out-of-the-box thinking for clinical trial design.

April 2022 Draft Guidance Regarding Diversity in Clinical Trials

The 2022 Draft Guidance is the FDA's latest effort regarding diversity in clinical trials and expands on its previous guidance to again encourage sponsors and stakeholders to address the racial and ethnic inequities in clinical trials by improving enrollment of participants from underrepresented racial and ethnic populations. The 2022 Guidance was prepared by the FDA's Oncology Center of Excellence (OCE) in collaboration with other centers and the Office of Minority Health and Health Equity (OMHHE), and applies to all drug, biologic and medical devices for which clinical studies are intended to support a marketing submission.[16]

As its name suggests, *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials*, the hallmark of the FDA's 2022 Draft Guidance[17] is its recommendation that sponsors of drugs and medical devices develop and provide a Race and Ethnicity Diversity Plan ("Plan") to enroll more participants in clinical trials from underrepresented racial and ethnic populations in the U.S. when submitting investigational new drug (IND) applications for drugs and biologics, or investigational device exemption (IDE). The goal of increasing the enrollment of underrepresented populations in clinical trials, such as Black or African American, Hispanic/Latino, Indigenous and Native American, Asian, Native Hawaiian and Other Pacific Islanders, and other persons of color, is to ensure that the data generated reflect the racial and ethnic diversity of the population that is expected to use the medical product. In addition, such inclusion could potentially identify effects on the safety or efficacy of outcomes that may be unique or occur more frequently in one or more of these populations. In an accompanying press release, FDA Commissioner Robert M. Califf, M.D. stated, "[t]he U.S. population has become increasingly diverse, and ensuring meaningful representation of racial and ethnic minorities in clinical trials for regulated medical products is fundamental to public health. . . . Going forward, achieving greater diversity will be a key focus throughout the FDA to facilitate the development of better treatments and better ways to fight diseases that often disproportionately impact diverse communities."[18]

The Plan should be discussed with the FDA "as soon as practicable"[19] during medical product development, but no later than when a sponsor is seeking feedback regarding the applicable pivotal trial for the drug (end of Phase 2 meeting). For medical devices, sponsors should submit their Plan as part of the IDE application. The FDA allows some flexibility and appreciates that recruitment goals may not be met despite best efforts, and recommends that sponsors should also discuss with the FDA a plan to collect data about the safety and effectiveness of the product in diverse populations in the post-marketing setting. While not meant to be exhaustive, the 2022 Draft Guidance sets forth the following five elements that sponsors should include in their Plan to improve diversity in clinical trials or studies:[20]

1. Overview of the disease/condition
    - Assess the available data on the pathophysiology of the disease or condition that provides the rationale that may affect the safety and effectiveness of the medical

product in underrepresented racial and ethnic populations.

2. Scope of the medical product development program
    - Describe the trials and how they may specifically address inclusion of underrepresented racial and ethnic populations, such as differential findings from clinical pharmacology studies (PK/PD studies) that may be associated with these populations.
3. Goals for enrollment of underrepresented racial and ethnic participants
    - Define and justify the planned enrollment of participants from underrepresented racial and ethnic populations. When epidemiology alone is not sufficient to detect any differences in safety and effectiveness, consistent representative enrollment may provide opportunities for pooling data to evaluate outcomes by race and ethnicity.
4. Specific plan of action to enroll and retain diverse participants
    - Describe operational measures to enroll and retain underrepresented racial and ethnic participants in planned trials including strategies such as site location and access, language barriers, sustained community engagement and other means to reduce trial burdens (e.g., frequency of procedures, using local resources and digital telehealth).
5. Status of meeting enrollment goals (as applicable)
    - Sponsors should reevaluate and update the Plan as progress is made. Sponsors should also discuss a plan and justification for collecting data in the post-marketing setting if enrollment goals are not met.

The FDA is rethinking the traditional approach to clinical trials and recognizes that decentralized health care is becoming the future, including decentralized clinical trial conduct.[21] Although the 2022 Draft Guidance focuses on race and ethnicity, the FDA does recommend sponsors also consider other underrepresented populations defined by demographics such as sex, gender identity, age, socioeconomic status, disability, pregnancy status, lactation status and comorbidity. As with all FDA guidance, this draft—if finalized—will contain nonbinding recommendations and represents the FDA's current view on the topic, but does not have the force and effect of law.

The DEPICT Act

Notably, the 2022 Draft Guidance was released shortly after the introduction of bipartisan legislation to increase diversity in clinical trials by requiring enhanced data reporting on clinical trial demographics and providing resources to improve access to clinical trials. Specifically, Rep. Anna G. Eshoo (D-CA), Chairwoman of the Energy and Commerce Health Subcommittee, Rep. Brian Fitzpatrick (R-PA) and Rep. Robin Kelly (D-IL) introduced the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act on February 3, 2022.[22] As proposed, the DEPICT Act would "require" sponsors to submit a diversity action plan with IND and IDE applications. Sponsors would be required to report clinical trial enrollment targets by demographic subgroup, including age, race, ethnicity and sex, and provide a rationale for "how the sponsor will meet such targets, including demographic-specific outreach and enrollment strategies, study-site selection, clinical trial inclusion

and exclusion practices, and any diversity training for trial personnel." The pending legislation would also authorize the FDA to "mandate postapproval studies or postmarket surveillance" when sponsors fail to meet diversity enrollment targets and do not provide a sufficient justification.

The practical realities of the proposed DEPICT Act need to be considered. In prepared testimony released ahead of the March 17, 2022 House Energy and Commerce Committee Subcommittee on Health hearing, Lucy Vereshchagina, PhD, vice president of science and regulatory advocacy for the Pharmaceutical Research and Manufacturers of America (PhRMA), cautioned that while PhRMA shares the goals of increasing diversity in clinical trials,[23] "policies that would create additional mandates for sponsors would have serious unintended consequences of reenforcing [sic] rather than overcoming known barriers to participation for patients including: unfeasibly large and long studies, delayed access to medicines, or disincentives for industry to invest in highly risky therapeutic areas."[24] These potential unintended consequences will ultimately be weighed against potential benefits. Ruben Mesa, MD, executive director of the Mays Cancer Center at UT Health San Antonio MD Anderson in his prepared testimony stated, "the DEPICT Act would provide critical trial enrollment and education resources to community health care providers to break down the barriers between academic trial sites and the community providers patients trust. . . . providing federal grants directly to community health centers serving underrepresented groups—allowing them to hire and train trial facilitation staff . . . necessary to seamlessly educate and enroll patients."[25]

Conclusion

The FDA's recent guidances represent an important effort to address inequities by increasing participation of underrepresented populations in clinical trials and ultimately improving our nation's health in the face of changing demographics. Notably, PhRMA's recently published principles reflect its member companies' voluntary commitment to enhancing diversity in future clinical trials. All stakeholders including industry, patient and community organizations, medical providers, policymakers and regulators will need to work together to address the existing challenges of racial and ethnic inequities to improve diversity and inclusion in clinical trials.

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FOOTNOTES

[1] *See* FDA, *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry*; *Availability* (Apr. 2022), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations. *See* also *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry; Availability*. 87 Fed. Reg. 22211-01 (Apr. 14, 2022).

[2] *See* for example Ramamoorthy A. et al., Racial/ethnic differences in drug disposition and response: review of recently approved drugs. Clin. Pharmacol. Ther., 97(3), 263-273 (2015). (Showing that 21% (35/167) of new molecular entities (NMEs) approved by the FDA between 2008-2013 reported racial/ethnic differences in pharmacokinetics, safety, efficacy, dosing, or pharmacogenetics.)

[3] Mai-Trang N. Dang et al., *The Influence of Ethnicity on Warfarin Dosage Requirement*, Ann. Pharmacother., 39(6), 1008-12 (2005). (Warfarin dosing requirements were highest in African Americans, intermediate in Whites, and lowest in Asians. The average maintenance dose of warfarin to achieve a target international normalized ratio (INR) of 2–3 for the time it takes plasma to clot was

6.1 mg in African Americans, 5.1 mg in Whites, and 3.4 mg in Asian Americans.)

[4]*See* U.S. Census Bureau, *Quick Facts* (July 1, 2021), https://www.census.gov/quickfacts/fact/table/US/PST045221 (Population estimates by race and Hispanic origin: White alone (not Hispanic or Latino) 59.3%, Black or African American 13.6%, American Indian and Alaska Native 1.3%, Asian 6.1%, Native Hawaiian and Other Pacific Islander 0.3%, Hispanic or Latino 18.9%.)

[5]*See* FDA, *2020 Drug Trials Snapshots Summary Report* (Feb. 2021), https://www.fda.gov/media/145718/download.

[6]*See* The National Institutes of Health Revitalization Act of 1993, signed into law on June 10, 1993, Pub. L. 103-43 (Public Health Service Act § 492B, 42 U.S.C. § 289a-2). *See* also National Institutes of Health. NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, 59 Fed. Reg. 14508-01 (Mar. 28, 1994).

[7] *See* 21st Century Cures Act, Pub. L. 114-255, 130 Stat. 1033 (2016). (Section 492B(c) requires the NIH Director to "ensure that the trial is designed and carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial." 42 U.S.C. § 289a-2(c)(1)).

[8] Food and Drug Administration Safety and Innovation Act, Pub. L. 112-144, 126 Stat. 993, 1092-93 (July 9, 2012). (Section 907 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) directed the FDA to publish and provide to Congress a report "addressing the extent to which clinical trial participation and the inclusion of safety and effectiveness data by demographic subgroups, including sex, age, race, and ethnicity, is included in applications submitted to the Food and Drug Administration.")

[9]*See* FDA, *FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data*, (Aug. 2014), at 2, https://www.fda.gov/downloads/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/UCM410474.pdf. (The FDA developed an action plan identifying three overarching priorities—quality, participation and transparency. "**Priority One:** Improve the completeness and quality of demographic subgroup data collection, reporting and analysis (**Quality**). **Priority Two:** Identify barriers to subgroup enrollment in clinical trials and employ strategies to encourage greater participation (**Participation**). **Priority Three:** Make demographic subgroup data more available and transparent (**Transparency**)".)

[10] See FDA, *Drug Trials Snapshots*, https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots.

[11]*See* FDA, *supra* note 6.

[12]*See* FDA, *Collection of Race and Ethnicity Data in Clinical Trials* (Oct. 26, 2016), at 1,

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/collection-race-and-ethnicity-data-clinical-trials. (This guidance provides the FDA's views and recommendations on "use of a standardized approach for collecting and reporting race and ethnicity data in submissions for clinical trials for FDA regulated medical products conducted in the United States and abroad" and

addresses the Action Plan under FDASIA Section 907 to improve demographic subgroup gaps in data quality.)

[13] 21 C.F.R. § 312.47(b) ("FDA has found that meetings at the end of Phase 2 of an investigation (end-of-Phase 2 meetings) are of considerable assistance in planning later studies . . .").

[14]*See* FDA, *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry* (Nov. 2020), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial.

[15]*See* FDA, *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products* (March 2019), at 1, https://www.fda.gov/media/121320/download. (Enrichment is defined as "the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population.")

[16] *See* FDA, *supra* note 1.

[17] See FDA, supra note 1.

[18]*See* FDA, *FDA Takes Important Steps to Increase Racial and Ethnic Diversity in Clinical Trials* (Apr. 13, 2022), https://www.fda.gov/news-events/press-announcements/fda-takes-important-steps-increase-racial-and-ethnic-diversity-clinical-trials.

[19]*See* FDA, *supra* note 1 at 2.

[20] *Id.* at 6-9.

[21] *See* FDA, *Advancing Oncology Decentralized Trials Modernizing Evidence Generation* (July 27, 2022), https://www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trials (The FDA plans to evaluate datasets to determine the utility of using remote assessments from the usual trial site assessments in clinical trials. "Decentralized Clinical Trials (DCT) hold promise to reduce patient and sponsor burden and increase accrual and retention of a more diverse trial population….")

[22]*See* Diverse and Equitable Participation in Clinical Trials Act (DEPICT), H.R. 6584, 117th Cong. (2022), https://www.congress.gov/bill/117th-congress/house-bill/6584/text?r=8&s=1.

[23]*See* Pharmaceutical Research and Manufacturers of America (PhRMA), *Principles on Conduct of Clinical Trials & Communication of Clinical Trial Results* (Nov. 2020), https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/P-R/PhRMAPrinciples-of-Clinical-Trials-FINAL.pdf. (PhRMA and its member companies added a new chapter to its Principles, "Commitment to Enhancing Diversity in Clinical Trial Participation." These are the first-ever industry-wide principles on clinical trial diversity, which became effective in April 14, 2021, reinforcing PhRMA member companies' efforts and reflecting their voluntary commitment to enhancing diversity in clinical trials. The principles for the conduct of clinical research are set forth as: 1) Commitment To Protecting Research Participants, 2) Conduct of Clinical Trials, 3) Ensuring Objectivity In Research,

4) Providing Information About Clinical Trials, 5) Expanded Access To Investigational Drugs, and 6) Commitment to Enhancing Diversity in Clinical Trial Participation.)

[24] *See* Testimony of Lucy Vereshchagina, PhD, Vice President, Science and Regulatory Advocacy

Pharmaceutical Research and Manufacturers of America (PhRMA), https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/Witness%20Testimony_Vereshchagina_HE_2022.03.17.pdf.

[25]*See* Testimony of Dr. Ruben Mesa, Executive Director, Mays Cancer Center at UT Health San Antonio MD Anderson, https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/Witness%20Testimony_Mesa_HE_2022.03.17.pdf.

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