October 10, 2023

Robert M. Califf, M.D.
Commissioner
U.S. Food and Drug Administration
Docket No. FDA-2022-D-2629
5360 Fishers Lane
Room 1061
Rockville, MD 20852

Re: FDA-2022-D-2629: Post-marketing Approaches to Obtain Data on Under-Represented Populations in Clinical Trials; Draft Guidance for Industry; Availability (August 11, 2023)

Dear Commissioner Califf:

The American Cancer Society Cancer Action Network (ACS CAN) appreciates the opportunity to comment on Post-marketing Approaches to Obtain Data on Under-Represented Populations in Clinical Trials; Draft Guidance for Industry (Draft Guidance). ACS CAN advocates for evidence-based public policies to reduce the cancer burden for everyone. As the American Cancer Society's nonprofit, nonpartisan advocacy affiliate, ACS CAN is making cancer a top priority for public officials and candidates at the federal, state, and local levels. By engaging advocates across the country to make their voices heard, ACS CAN influences legislative and regulatory solutions that will end cancer as we know it. We are providing comments on the draft guidance through the lens of cancer patients, for whom equitable drug development and clinical trials are a key factor in providing effective treatment.

We applaud FDA's commitment to ensuring participation of diverse populations in clinical trials, especially among historically under-represented groups. ACS CAN previously supported FDA's guidance on enhancing trial diversity,[1,2] and this call was echoed in our recent recommendations for Equitable Discovery and Implementation of Pharmacogenomic Testing in Cancer Care.[3]

Race, Ancestry, and Under-Represented Populations

Variation in responses to a given drug among individuals can be based on various extrinsic and intrinsic factors. Extrinsic factors may include local medical practices, diet, environmental factors, smoking, and alcohol or other drug use. Intrinsic factors may include weight, sex, age, and genetics. As noted in FDA's 2020 guidance[1], considering these factors when designing and enrolling for clinical trials is critical to understanding interpatient variability in the effectiveness and toxicity of a drug.

One specific intrinsic factor known to affect drug response is genomic variants that encode proteins that play a role in the metabolism or transport of drugs. Genetic variation manifests in individuals who inherit their genomic makeup via their ancestral lineage. Populations that share genetic ancestry tend to share specific genetic variants, contributing to population-based differences in disease incidence and drug metabolism. In research and medicine, however, genetic ancestry is typically replaced by the more commonly used demographic categories of race, region, and ethnicity, which are usually self-reported values that do not directly correspond to genetic ancestry. The use of race or ethnicity as a proxy for genetic ancestry can support erroneous assumptions about genetic homogeneity, and in the clinic can lead to genetic misdiagnosis and adverse drug reactions.[4]

Pharmacogenomics (PGx) is the study of such interactions between inherited genomic variation and clinical effectiveness of drug response. Identification of PGx drug-gene interactions generally requires drug administration at relevant doses, observable clinical response (phenotype), genetic information to identify gene variants (genotype), and sufficient numbers of patients to evaluate potentially rare variants. Although FDA has called in its draft guidance to increase diversity when designing and enrolling patients for clinical trials to understand interpatient variability in the effectiveness and toxicity of a drug, the lack of enrollment of participants with diverse genetic ancestry (notably not merely diverse based on "race" or other socially constructed groupings) makes discovery of new PGx relationships, especially in historically under-represented populations, unlikely.[1,5]

Importance of Including Under-Represented Populations in Cancer Drug Development and Testing

Thus, to be effective, it is important for trials to include subpopulations representing diverse genetic ancestry groups, rather than presuming genetic similarity based on "race." Furthermore, representation in clinical trials is important for patient confidence in the safety and effectiveness of drugs, even after FDA approval. In 2023 ACS CAN conducted a survey of over 1,000 cancer patients and survivors nationwide, in which 72% of respondents indicated confidence in the FDA drug approval process. However, 25% of respondents indicated that they would lose confidence in a drug if the clinical trial leading to the drug's approval didn't include participants whose race and ethnicity matched the respondent. The level of concern was significantly higher among Black respondents with 60.6% indicating that such a mismatch would cause a loss of confidence (www.fightcancer.org/policy-resources/survivor-views-composition-clinical-trials).

Typical premarket registrational studies are unlikely to identify drug-gene associations for genes with low variant frequency, even if a diverse population is enrolled, given the relatively small trial sizes in oncology. Evaluation of larger-scale post-marketing data may be needed to characterize potential PGx liabilities.[6] We support the recommendations in the draft guidance for obtaining postmarket safety and effectiveness information on drugs in historically under-represented populations, when that information was not able to be obtained in premarket research. These goals align with our recent recommendations for Equitable Discovery and Implementation of Pharmacogenomic (PGx) Testing in Cancer Care[3], particularly Recommendation #1:

> Sponsors should ensure diverse ancestral group participation in clinical trials per the epidemiology of the disease in alignment with existing FDA guidance on inclusion of racial and ethnic groups. Data or samples that can be used to evaluate interactions with potential pharmacogenes should be collected. In cases

where prior evidence has suggested potential PGx impacts, especially differential impacts between subgroups, research plans should be formulated to clearly define such differences. FDA should provide additional guidance for methods outside of registrational trials for exploring PGx differences, such as using in-vitro assays, mining genetic databases, collecting real-world data (RWD), or other methods.

Postmarket studies and clinical trials

Postmarketing requirements (PMRs) and commitments (PMCs) to collect data on under-represented populations may face similar challenges to premarket research. Although most cancer patients express a willingness to participate in clinical research, only a small fraction ultimately end up enrolling in a cancer clinical trial due to barriers that make participation difficult or even impossible.[7] While all patients face barriers to enrolling in cancer clinical trials, certain groups face even greater barriers than others, and the largest barriers preventing trial participation are generally outside of a patient's control. A recent meta-analysis of enrollment barriers to cancer clinical trials found that local trial availability prevented 55.6% of patients from taking part in trials, and eligibility criteria on average keep 21.5% of patients from enrolling in clinical trials, suggesting that how a trial is designed and where it is conducted play the biggest roles in facilitating enrollment.[8]

The suggestions in the draft guidance to collect postmarket safety and efficacy data on particular subpopulations can be most effective if enrollment barriers specific to the subpopulations in question are addressed. The draft guidance mentions clinical trial site selection as an example of a consideration to maximize enrollment and refers to previous guidance for enhancing trial diversity for mechanisms to address barriers, which we previously supported.[1,2] Addressing barriers to enrollment in a manner specific to the subpopulation(s) being targeted is crucial in order to effectively enroll the cohort(s) in question. In our response to FDA's 2022 Diversity Plans to Improve Enrollment of Participants from Under-represented Racial and Ethnic Populations in Clinical Trials Draft Guidance for Industry,[9] we described two key barriers that diverse populations experience: the cost of trial participation, and the availability of local trials.[10] Cost barriers, which disproportionately affect under-represented U.S. populations, can be mitigated by ensuring support for financial reimbursement of non-medical expenses incurred by trial participants, such as travel or lodging. Barriers related to local trial availability may affect as many as 77% of patients who will not have a local trial available for their cancer.[7] Decentralized trials, use of local resources such as labs and clinics, and telehealth technologies are all avenues that can help address this barrier. Importantly, these barriers will need to be addressed for postmarket data collection via interventional studies to be effective.

Use of Real-World Data

Real-world data (RWD) can be an important source of information for postmarket data collection; however, as the draft guidance notes, "multiple complex issues" arise when seeking data on under-represented populations. EHR data regarding genetic ancestry may be uninformative or inaccurate if the record is based on self-reported "race", or includes demographic information based on provider interpretation of visible markers of ancestry, such as skin color.[11,12] Other data repositories contain extensive genomic information on large populations, but historically, these databases have been primarily composed of individuals of European ancestry.[4] We encourage FDA to define these issues

related to under-represented populations and RWD in the final guidance, and to address them clearly in postmarket research planning discussions. RWD may be more effective in detecting signals of concern rather than providing definitive evidence of subgroup differences.

Use of Foreign Clinical Data

In oncology, close to two-thirds of clinical trial participants in U.S. drug approval applications come from outside the U.S., where the demographic makeup is significantly different.[13] The draft guidance acknowledges that when a marketing application was based on data obtained from clinical trials conducted outside the U.S., postmarketing studies may be needed involving participants representative of the diversity of the U.S. population. It is important to note, however, that even if non-U.S. trials enroll subpopulations that are genetically reflective of similar ancestry groups in the U.S. (i.e., have intrinsic similarities), extrinsic factors such as diet, lifestyle, comorbidities, and access to health care may vary from those experienced by populations in the U.S. Differential outcomes among study groups may be due to extrinsic, rather than intrinsic factors. Moreover, 37% of ACS CAN survey respondents reported that they would lose confidence in an FDA-approved drug if it had not been tested in U.S. residents (www.fightcancer.org/policy-resources/survivor-views-composition-clinical-trials). We encourage FDA to provide more clarity in the guidance about the use of foreign clinical data and its ramifications on ensuring appropriate representation.

Inclusion of Population-Specific Data in Drug Labels

We support the addition of clinically-relevant information to drug labeling, especially when data concerning populations of shared genetic ancestry suggests a unique risk or response. In order for this information to be most useful and accessible, we have recommended that FDA make efforts to improve the consistency, completeness, and location of drug label information (see PGx recommendations #3a and 3b).[3] For example, according to FDA, the location of PGx information can appear in various FDA-approved drug label sections depending on the actions that can be taken.[14] Different drugs with the same drug-gene interaction may list PGx information in different sections of a label; the same drug in different formulations may offer different PGx considerations; and while some drug labels provide information on carrier frequency across various populations (e.g., race, ethnicity, ancestry) for a given gene variant with PGx implications, other drugs with population effects do not.[15]

According to the draft guidance, postmarketing studies are indicated "if there is data to suggest a signal of a serious risk" to members of a population or subgroup. When this premarket data is sufficient, we encourage FDA to add language to drug labeling indicating preliminary indication of possible risk and the decision to initiate postmarketing studies.

Conclusion

This draft guidance builds on previous FDA guidance issued in 2020 to enhance the diversity of participants in clinical trials and recognizes the importance of a range of efforts to ensure that diverse populations are represented. These efforts are especially relevant for those who are at risk of a differential drug response due to their genetic ancestry, and we support postmarket mechanisms to obtain this information and make it available in drug labeling. Thank you for the opportunity to

comment on this draft guidance. If you have any questions, please feel free to contact me or have your staff contact Mark Fleury, PhD (mark.fleury@cancer.org), Principal, Policy Development - Emerging Science.

Sincerely,

Lisa A. Lacasse, MBA
President
American Cancer Society Cancer Action Network

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[1] Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2020) Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry https://www.fda.gov/media/127712/download

[2] ACS CAN comments on FDA Guidance: Enhancing the Diversity of Clinical Trial Populations, dated August 6, 2019, accessed at: https://www.fightcancer.org/policy-resources/comments-fda-guidance-enhancing-diversity-clinical-trial-populations

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[10] ACS CAN Comments on Draft FDA Guidance on Clinical Trial Diversity Plans. Letter dated June 13, 2022. https://www.fightcancer.org/policy-resources/acs-can-comments-draft-fda-guidance-clinical-trial-diversity-plans

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