American Association for Cancer Research®
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February 28, 2020

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2019-N-4824 Priorities for the U.S. Food and Drug Administration's Office of Minority Health and Health Equity

To Whom It May Concern:

On behalf of the American Association for Cancer Research (AACR), the first and largest scientific organization in the world dedicated to the prevention and cure of cancer through research, education, communication, and collaboration, we sincerely thank the U.S. Food and Drug Administration (FDA) for the opportunity to provide feedback in response to the request for comments on Priorities for the FDA's Office of Minority Health and Health Equity (OMHHE). The membership of the AACR includes more than 46,000 basic, translational, and clinical researchers working in both academia and industry; population scientists; other health care professionals; regulators; and patient advocates residing in 127 countries. We share OMHHE's commitment to promoting and protecting the health of diverse populations through research and communication of science that addresses health disparities, specifically disparities in cancer incidence and mortality.

Indeed, the AACR recently partnered with the FDA Oncology Center of Excellence to cosponsor a workshop to address the under-representation of African Americans in multiple myeloma clinical trials compared to disease incidence. In advance of the workshop, researchers, clinicians, physicians, patients, representatives from the pharmaceutical industry, and regulators—including OMHHE staff—worked together to develop recommendations for improving the representation of African Americans in all phases of clinical and post-marketing studies of multiple myeloma. Due to racial differences in disease biology and incidence, this is imperative to better understand drug safety, efficacy, and outcomes in African Americans, and to improve the generalizability of multiple myeloma clinical trial results.

This initiative was put forth to address the unfortunate reality that African Americans represent 13 percent of the U.S. population and 20 percent of individuals diagnosed with multiple myeloma, yet account for only 4.5 percent (median) of multiple myeloma pivotal trial enrollees (Bhatnagar et al. Blood 2017). Despite the specific focus of our initiative, we believe many of our recommendations can be applied broadly to any disease or malignancy with a disproportionate racial or ethnic burden. We have shared a subset of these recommendations for your consideration below.

Efforts that generate clinical evidence to improve the generalizability of clinical trial findings and bridge the knowledge gap about the medical products' performance in racial and ethnic minority populations.

<u>Clinical Trials</u>

- Liberalize eligibility criteria for clinical trials whenever possible and appropriate.

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    - When eligibility criteria for registrational trials are more conservative, postmarketing studies of those agents should have liberalized eligibility criteria so populations who use the agents in the real world are better represented.
    - Additionally, sponsors should consider approaches that utilize expansion cohorts with liberalized eligibility criteria within registrational trials to assess feasibility/tolerability and to collect more data in racial and ethnic subpopulations.
- Require sponsors to complete a specific, prospective "study plan" that outlines how an appropriately diverse population will be included in the trial and set concrete targets for trial enrollment based on disease epidemiology/incidence.
    - Describe in the study plan, with detailed strategies, how representativeness and inclusion targets will be met for recruitment, accrual, and retention including approaches that will be employed to overcome cultural barriers.
        - Encourage sponsors to hit set targets in premarket trials.
            - Prespecify what subgroup analyses should be performed and the endpoints, which will be assessed. Potentially ask for modeling on the effects of having more or fewer patients than expected for a given subgroup.
            - Explore potential alternative endpoints.
        - Require sponsors to set prospective plans for how to meet targets in the postmarket setting if goals are not met in the premarket trials.
        - If plans include the use of real-world data, sponsors should prespecify what analyses will incorporate those data and recognize the lack of randomization to control for unknown confounders.
    - Recommend that FDA review divisions assure study plans are in place and ask sponsors to monitor targets.
- Share examples of strategies employed by those conducting trials that helped meet target enrollment in subpopulations.
- Appoint a "diversity officer" to each phase II and phase III clinical trial to help design the trial and recruitment strategies for achieving the prespecified goals of representativeness and inclusion outlined in the study plan. The diversity officer role should be defined, and training offered to sponsors and investigators on what would constitute a qualified diversity officer.
- Educate clinical investigators and physicians who may refer patients to clinical trials on the importance of representativeness and inclusion in trials and provide training on cultural competence toward that end.
- Data on racial outcomes should be gathered early and throughout development, when feasible, to inform later investigations.
    - Collect genomic data with updated ICH guidelines to establish bases for differences in outcomes.
    - Emphasize the importance of prospectively collecting this data to investigators. Ex-U.S. trial sites may have confidentiality laws that do not allow reporting on or collecting race/ethnicity data.

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- Discuss, determine, and disseminate a common reporting framework for diseases and malignancies with minimum data elements and reporting format that includes race and ethnicity that all stakeholders accept as the minimal amount of data that should be collected and abstracted.

Postapproval Strategies

- Conduct prespecified analyses to identify differences among subpopulations defined by race and ethnicity when there is a safety signal or question about the efficacy.
    - Exploratory analyses should be described in the trial protocol.
    - If safety signals are detected or insufficient data are generated in registrational trials, it may be necessary to carry out a pilot study or expansion cohort of a phase I trial in African Americans (subpopulation of interest) to generate data necessary to test the hypothesis that there are PK/PD differences among races/ethnicities.
- Pool or merge data across pharmaceutical industry or cooperative group studies of older drugs to aggregate sufficient numbers for racial and ethnic subpopulations to perform exploratory analyses that assess safety and efficacy.
- Design postapproval studies to retrospectively collect data from patients who received standard of care therapy versus experimental therapy to better account for selection bias.
- If evidence from meta-analyses or real-world data indicates the need to investigate a critical hypothesis about how a cancer drug may work differently in a patient subpopulation, further evaluation should be undertaken, preferably by means of a randomized trial.
    - If the conduct of a randomized trial is not feasible, practical, or timely, prospective studies should be conducted, or the use of existing real-world data should be used for further assessment that can contribute to the understanding of the causal inference in convincing fashion.
- Use real-world data to study efficacy and tolerability in specific subpopulations, which could, in turn, generate hypotheses for clinical trials enriched for that subpopulation.
    - Describe an ideal registry and determine the minimum data elements to ask and answer pertinent questions.

Performing direct outreach to racial and ethnic minority, underrepresented, and underserved populations (e.g. raising awareness on the inclusion of racial and ethnic minority populations in clinical trials).

- Stakeholders should devise strategies to address clinical, social, and socioeconomic impediments to trial access. Forge partnerships through outreach to include pharmaceutical companies, social groups not traditionally approached for trial enrollment, e.g., barbershops, churches, sororities/fraternities, and medical societies.
- Engage directly with patient groups to build trust and encourage participation in trials and registry studies.
    - Encourage patients to share their trial experiences with others considering clinical trials can help alleviate fears or concerns about joining a trial.

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Identification of opportunities for collaboration to generate efforts to address research gaps that predominantly affect racial and ethnic minority populations.

- Develop precompetitive programs that make resources available to support/establish clinical trial infrastructure in treatment locations that are race/ethnicity rich but have not traditionally been part of the clinical trial ecosystem.
- Provide grant funding dedicated to studying subpopulation signals.

Additional recommendations from our initiative that align closely with OMHHE's goal of eliminating health disparities and achieving health equity are outlined in the "FDA-AACR Workshop to Examine Under-representation of African Americans in Multiple Myeloma Clinical Trials Discussion Draft" disseminated at our meeting and available here (link: https://www.aacr.org/wp-content/uploads/2020/02/Discussion-Draft.pdf). In follow up from the workshop, we are accepting public feedback and comments to inform our final recommendations, which will be published in a peer-reviewed academic publication in the future.

Moreover, on March 25, 2020, the AACR will release its inaugural Cancer Disparities Progress Report to Congress in Washington, DC. The inaugural AACR Cancer Disparities Progress Report to Congress and the American public is a cornerstone of the AACR's educational and advocacy efforts in the field of cancer health disparities. The report highlights areas of progress in reducing cancer health disparities. It also emphasizes the vital need for continued transformative research and for increased collaboration among all stakeholders working toward the bold vision of health equity if we are to ensure that research-driven advances benefit all people, regardless of their race, ethnicity, age, gender, sexual orientation, socioeconomic status, and the community in which they live. This report builds on the AACR's longstanding leadership efforts to advance our shared goal of understanding, and ultimately, helping to eliminate cancer disparities in racial and ethnic minorities and other underserved populations. We cordially invite staff from OMMHE to attend our informational Congressional briefing on March 25, 2020, and after, we will follow up with your office to share this historic report with you.

In closing, this work is part of our greater responsibility to create a more inclusive, real-world paradigm for drug development. With trial populations that are more representative of real-world patients, everyone will feel more comfortable with new therapies. The AACR is encouraged by the OMMHE's deliberate, proactive efforts to promote innovative and effective drug development with the goal of ensuring all patients have access to the best therapies available. We look forward to continued engagement with OMMHE as areas of policy and guidance development are identified. If you have further questions, please contact Sarah K. Martin, MS, PhD, Director, Regulatory Science and Policy, at sarah.martin@aacr.org.

Sincerely,

Kenneth C. Anderson, MD
Chair, Regulatory Science and Policy Subcommittee
American Association for Cancer Research

Margaret Foti, PhD, MD (hc)
Chief Executive Officer
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