February 28, 2020

The Honorable Stephen M. Hahn, MD
Commissioner
Food and Drug Administration
Dockets Management Staff (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Office of Minority Health and Health Equity Strategic Priorities; Establishment of a Public Docket; Request for Comments (FDA-2019-N-4824)

Dear Commissioner Hahn:

The American Cancer Society Cancer Action Network (ACS CAN) appreciates the opportunity to comment on the U.S. Food and Drug Administration's (FDA's) Office of Minority Health and Health Equity (OMHHE) Strategic Priorities public docket (FDA-2019-N-4824). An important aspect of addressing cancer health disparities is understanding to what degree disparate health outcomes may be driven by differential responses to therapeutic drugs and devices. FDA sits in a unique position to drive progress in this area, since it often has access to proprietary data not in the public domain. Additionally, FDA influences the design of clinical trials that could collect important data helpful to better understanding disparities.

New drugs and devices meant to diagnose, treat, or prevent cancer must first undergo review and approval by the FDA prior to being made commercially available. FDA reviews data generated from clinical studies in which the product is tested to evaluate the benefit-risk ratio for its intended use. By design, clinical trials exclude many patients to protect the safety of participants and minimize confounding factors that may affect patient outcomes. The result is a trial population that does not necessarily reflect the intended population for the treatment, with the trial participants generally skewing younger, healthier and less diverse. When drugs are approved and move into broader use, the real-world patient outcomes often do not match those observed in clinical trials due to these differences in patient characteristics. While minor differences in trial and real-world outcomes are not unusual, large overall differences, or large subgroup differences are concerning, especially since the latter can lead to disparities in outcomes.

One of the stated areas of interest for this request for comments is how to improve generalizability of clinical trial findings and bridge the knowledge gap about the medical products' performance in racial and ethnic minority populations. Several overarching issues merit the focus of OMHHE and are characterized below.

Trials Outside the U.S.

Most registrational trials for oncology drugs occur outside of the U.S.[1], where diets, health systems, and lifestyle factors may be very different than in the U.S., and all these factors have

been shown to affect patient outcomes. Recently, even the microbiome of individuals, which can vary greatly with diet, has been shown to modulate effectiveness of certain immunotherapies[2]. OMHHE could provide important research into how non-U.S. trial data corresponds to U.S. real-world outcomes, causes for any differences, and how any differences might specifically lead to disparate outcomes among disadvantaged populations here in the U.S.

It is notable that although there have been efforts to improve participation of underrepresented groups in research from the design phase through participation in clinical trials, the high proportion of cancer trials conducted outside the U.S. make it nearly impossible to recruit a trial population reflective of the U.S. population. This is especially true for individuals of African descent since the ex-U.S. cancer trials are commonly conducted in Europe or Asia[1] where populations are frequently less diverse.

Relevance of Drug "Snapshots"

While proportional representation is rarely achieved in oncology clinical trials, even when it is, subgroup analyses are often not possible because of the overall size of registrational trials. Trials are typically only as large as necessary to demonstrate therapeutic superiority in the whole group receiving an intervention, which frequently may involve only a few hundred patients, meaning that relevant subgroups may only include a handful of patients. For the past several years FDA has created drug "snapshots" meant to provide transparency into the composition of clinical trial participants for the trials used to approve new drugs as well as indicate when there are different outcomes based on demographic subgroups[3]. Within oncology, these snapshots have provided a window into participant makeup, but more often than not they indicate that racial subgroup analysis is not possible because of small trial sizes.

Oncology drug approvals often show an overrepresentation of Asians relative to the U.S. population with cancer, so this is one subgroup where racial subgroup analyses are sometimes possible. This over representation is typically due to clinical trials conducted entirely in Asia, as opposed to including Asian Americans. It is unclear whether any insights gained from subgroup analyses between Asians living in Asia and whites would be applicable to expected differences between white and Asian-Americans given different diets, lifestyles and medical systems. Since the snapshots are targeted at a U.S. population, OMHHE should investigate the applicability of performing such comparisons.

Asians are not a homogenous group, with differences in cancer incidence, subtype and outcomes between Asian subgroups (e.g. Japanese, Chinese, Korean, Filipino)[4,5]. It is unclear if even attempting to analyze differences using this pooled category is scientifically grounded or meaningful. OMHHE should investigate whether drawing inferences from pooled Asian subgroups leads to valid analyses of potential therapeutic or safety differences for any given Asian subgroup.

Identification of Factors Known to Impact Drug Metabolism, Safety or Efficacy

While trials are not required to be designed to be able to conduct subgroup analyses that could detect racial or ethnic outcome differences, evidence has nonetheless been generated in certain cases demonstrating differential responses to certain drugs or drug classes[6]. While not all the mechanisms are currently understood, OMHHE should catalog drugs and drug classes where known racial differences in response or metabolism exist and consider developing guidance that would ensure appropriately powered trials for subgroup analyses for drugs or drug classes where past evidence has suggested differential outcomes are likely to occur. OMHHE should consider additional research as needed to fill in evidence gaps in this space.

Summary

Finally, we would like to call your attention to a collaborative publication examining the barriers faced by cancer patients interested in enrolling in clinical trials. "Barriers to Patient Enrollment in Therapeutic Clinical Trials for Cancer: A Landscape Report" was published in 2018 and is an exhaustive examination of evidence about participation barriers, with a special section on disparities[7]. The report was accompanied by 23 consensus recommendations for overcoming the identified barriers. Since publication of the report, ACS CAN has continued to convene diverse stakeholders ranging from patient groups, to providers, institutions, individual researchers and government representatives in an effort to implement the recommendations. We encourage FDA to utilize the coalition to better understand stakeholder needs and capabilities.

Thank you again for the opportunity to provide comments, and we look forward to working with you to make sure that the fruits of our scientific innovation are available to all cancer patients. If you have any questions, please do not hesitate to contact Mark Fleury, PhD (mark.fleury@cancer.org), Principal, Policy Development - Emerging Science, and Phylicia Woods (phylicia.woods@cancer.org), Director of Federal Relations.

Sincerely,

Keysha Brooks-Coley
Vice President, Federal Advocacy & Strategic Alliances

References:

1-Kanapuru B, Singh H, Fashoyin-Aje LA, et al. FDA analysis of patient enrollment by region in clinical trials for approved oncological indications. J Clin Oncol. 2018;35(15_ suppl):2539. doi:10.1200/JCO.2017.35.15_suppl.2539

2-Matson V, Fessler J, Bao R, Chongsuwat T, et al. "The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients." Science05 Jan 2018 : 104-108

3-FDA Drug Snapshots, accessed at https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots

4-Chuang, E., Christos, P., Flam, A. et al. Breast Cancer Subtypes in Asian-Americans Differ According to Asian Ethnic Group. J Immigrant Minority Health 14, 754–758 (2012). https://doi.org/10.1007/s10903-012-9577-7

5-Pineda MD, White E, Kristal AR, Taylor V. Japanese have better breast cancer survival than other Asians Asian breast cancer survival in the US: a comparison between Asian immigrants, US-born Asian Americans and Caucasians." International Journal of Epidemiology, Volume 30, Issue 5, October 2001, Pages 976–982, https://doi.org/10.1093/ije/30.5.976

6-Sartor AO, Armstrong AJ, Ahaghotu C, et al. "Overall survival (OS) of African-American (AA) and Caucasian (CAU) men who received sipuleucel-T for metastatic castration-resistant prostate cancer (mCRPC): Final PROCEED analysis." Journal of Clinical Oncology 2019 37:15_suppl, 5035-5035

7-American Cancer Society Cancer Action Network. "Barriers to Patient Enrollment in Therapeutic Clinical Trials for Cancer: A Landscape Report." 2018. Available at www.fightcancer.org/clinicaltrialbarriers