April 29, 2016

The Honorable Robert Califf, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2015-N-4952, FDASIA 907 Public Meeting: Progress on Enhancing the Collection, Analysis, and Availability of Demographic Subgroup Data; Request for Comments

Dear Dr. Califf:

On behalf of our undersigned organizations, we appreciate the opportunity to participate in the FDA's recent public meeting on the status of implementation of the *FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data,* as required by Section 907 of the Food and Drug Administration Safety and Innovation Act (FDASIA). We were very pleased that you attended this meeting and that in your opening remarks you indicated your support for our goals outlined below. We submit the following comments in response to the meeting and the FDA's request for comments.

The Past

Our organizations have a long history of working with the Agency to address the low rates of participation by women, the elderly, and people of color, in clinical trials and ensuring that these populations are included in research in sufficient numbers as to allow for analysis. Adequate representation of these demographic subgroups in clinical trials is critical to ensuring that data exists to show that products are safe and effective for all patients. Our groups were the leading advocates behind Section 907 of FDASIA.

The Present

We applaud the FDA for the steps it has taken over the last 18 months to implement the Action Plan on demographic subgroup data. By declaring 2016 "the year of more diversity in clinical trials", the FDA is acknowledging that participation of women and people of color in clinical trials is vital to improving our understanding of how people in subgroups are affected by diseases and conditions. The Diverse Women in Clinical Trials initiative launched this year by the FDA's Office of Women's Health, in collaboration with the National Institute of Health's Office of Research on Women's Health, will raise awareness and share best practices about clinical research design, recruitment, and subpopulation analyses. We also recognize that FDA has taken further steps to implement the Action Plan, such as finalizing a number of updated guidance documents and updating the MedWatch forms to standardize the collection of demographic information on possible adverse events. These are positive steps towards achieving the gaps identified in the 2013 Report to Congress.

The Action Plan identified three distinct areas where work was needed: improving the completeness and quality of demographic subgroup data, identifying barriers and employing strategies to encourage greater subgroup enrollment in clinical trials and improving availability to the public of demographic subgroup data. The Drug Trials Snapshots (Snapshots) website, which was launched in December 2014, makes demographic data more available and transparent by providing health professionals and consumers with information about clinical trials for new drugs. Number and type of participants are shown, and differences in benefits and side effects by sex, race and age are noted. If there were not enough participants in a subgroup to draw conclusions, that is also indicated. As you pointed out in your January 27, 2016 blog, an FDA evaluation of the Snapshots program confirms that some groups, especially ethnic and racial groups, aren't always well represented in clinical trials. While racial and ethnic minorities were most consistently and significantly underrepresented, the Snapshots reveal that data are also often lacking for women and the elderly, when compared to men and younger age groups.

For example, a Snapshot for the drug Kengreal reveals that only 28 percent of the trial participants were women, indicating that women were not represented proportionately to the prevalence of coronary heart disease in women. In addition, since the majority of patients in the trial were white, differences in response to Kengreal among races could not be determined. While the Snapshot for the drug Savaysa revealed that the drug was similarly effective in whites and Asians, because the number of non-white, non-Asian patients in the trial was limited, it was not possible to determine whether there were clinically meaningful differences. The Snapshot for the drug Zontivity demonstrated that, while the risk of bleeding was higher among women taking this drug than men and that the drug increased the risk of bleeding in all age groups, there were too few non-Caucasian patients to make a reliable assessment of bleeding risk by race. The drug Corlanor appeared to be similarly effective in whites and Asians, but because of the limited number of black patients in the trial, differences in response for blacks could not be determined. More work must be done during the design phase of future trials to include more robust participation across age, sex and races, and acknowledgement of its importance must be reflected in the approval process. We note that the Snapshots program needs to be expanded to include earlier phases in clinical studies and also to include devices, where there remains an underrepresentation of women in clinical trials. Research has demonstrated that there are important sex differences in risks and benefit for drugs and devices.

The Future

We are encouraged by your commitment to work with the research community and with patient advocacy groups for the conduct and analysis of trials to engage patients and provide the best estimates of treatment effects for diverse populations. Like you, we are very committed to ensuring that the Action Plan is not just a plan that gathers dust on a shelf, but rather is a living document that guides FDA's work reviewing and approving medical products.

While the FDA has made good progress in implementing the short-term action steps, many of the intermediate and long-term actions are not yet completed. We look forward to working with FDA on the implementation of the remaining action steps. For example, in the area of completeness and quality of data, FDA is reportedly working on drafting guidance on the analysis and reporting of ethnicity, race, and age in medical device studies, similar to the guidance FDA released in 2014 with respect to sex, but this guidance has not yet been released in draft form. While we support the development of this guidance, we also want to emphasize that stronger enforcement of FDA's existing authority to require the reporting and analysis of subgroup information is needed. In addition, FDA still must clarify in its

new or existing guidance or regulations that *meaningful* subgroup analyses must be conducted and then this guidance must be enforced.

In the area of improving diversity, FDA indicated that it intends to work with industry on appropriate use of exclusion criteria. We understand that FDA has conducted training for its reviewers that encourages them to watch out for inappropriate drug trial exclusion criteria, yet more work is needed in this area. In particular, we request that FDA provide an update on how it plans to work with industry to address this important issue. In addition, according to section 2.3 of the plan, FDA intends to work with product sponsors to develop and share best practices for recruiting a broad representation of patients. Disseminating best practices is a step in the right direction, but achieving the goal of more diverse participation will only be realized if industry actually adopts best practices. Therefore, the FDA should go a step further and require study sponsors to proactively develop and submit evidence-based plans for enrolling sufficient proportions of women, people of color, and the elderly in trials. Periodic monitoring of enrollment by FDA and industry collaboratively can help achievement of these goals. We also think an FDA consumer update describing what it is like to participate in a clinical trial and encouraging the public to enroll in trials, as described in your January 27, 2016 blog, is a good idea.

With respect to greater transparency, continued improvements are needed to the Drug Trials Snapshots. As you know, the Society for Women's Health Research convened a workshop on "Achieving Meaningful Subgroup Data in Clinical Trial Design and Development: Scientific Considerations and Approaches" back in January that included a great deal of stakeholder discussion about how the Snapshots can be improved. We encourage the FDA to carefully review and adopt the consensus recommendations that came out of this workshop. On a related note, we understand that FDA is piloting a program to make demographic information available for biologics. We expect that this pilot can also benefit from the lessons that have been learned from implementing the drug Snapshots, and we also once again note the need for a similar program for devices.

The Action Plan also stated FDA's intention to explore potential methods for communicating meaningful information through product labeling. We do not know the status of this effort, but hope it will lead to the inclusion of improved, consistent information on a product's safety and efficacy in women, people of color, and the elderly in the labeling and use instructions.

Finally, our organizations intend to provide continued oversight to ensure that this important work continues. It is particularly critical that implementation continue as FDA transitions to a new administration. To help ensure that this is the case, we recommend that FDA take the following two steps:

- Your internal Section 907 steering committee should establish, publish and track on the Section 907 webpage specific metrics and timeframes that can be used to assess the implementation and outcomes of the Action Plan.
- We previously recommended that FDA put in place a system of real-time, transparent monitoring for specific trials, and we continue to believe such an initiative would be very helpful in ensuring that progress is being made to improve the diversity of trials. We would like to see this system in place and are happy to work with you on its implementation.

Conclusion

In closing, we appreciate the work that has occurred so far in implementing the Action Plan, and we are eager to work with FDA on its continued implementation. The results will be well worth the effort – medical products that are better targeted to the subgroups using them and a reduction in the health inequities for women, people of color, and the elderly.

If you have any questions or need any additional information, please do not hesitate to contact one of our staff: Stephanie Mohl, Senior Government Relations Advisor at the American Heart Association, at (202) 785-7909 or stephanie.mohl@heart.org; Sarah Christopherson, Program Director at the National Women's Health Network, at 202-682-2640 ext. 223 or schristopherson@nwhn.org; Leslie Ritter, Vice President, Public Policy at the Society for Women's Health Research (SWHR), at 202-496-5003 or Leslie@swhr.org; or Susan Campbell, Director of Public Policy at WomenHeart: The National Coalition for Women with Heart Disease, at 202-728-7199 or scampbell@womenheart.org.

Thank you for your consideration of our comments.

Sincerely,

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