October 21, 2014

The Honorable Margaret Hamburg, 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-2013-N-0745-0053, Comments on FDASIA Section 907 Action Plan

Dear Dr. Hamburg:

On behalf of our undersigned organizations we submit these comments on the recently released *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 commend the FDA, its medical product centers, and particularly the Office of Women's Health (OWN) and the Office of Minority Health (OMH) for their extensive work to develop the Action Plan.

With rapid implementation and consistent enforcement, these substantive directives could go a long way towards improving the diversity of clinical trials and the quality and availability of subgroup data and analysis. Ultimately over time, these improvements could address many of the health disparities that afflict women, minorities, and the elderly. As you know, FDA's own August 2013 report documented clear and continuing gaps in the participation of women, minorities, and the elderly in clinical trials, the analysis of subgroup differences, and the availability of subgroup-specific data to clinicians, researchers, and patients. We applaud the FDA for recognizing the deficiencies and laying out 27 recommended action steps, along with timeframes for their implementation. Even more can and should be done, however, to address these deficiencies. Therefore, we offer the following specific recommendations for your careful review and consideration.

Priority 1: Completeness and Quality of Data

We believe it is particularly important that the FDA establish and clearly articulate for application sponsors the consequences of not complying with regulations and guidance related to the inclusion of subgroups and the analysis and reporting of subgroup data. If subgroup representation is inadequate, and/or if the analysis is incomplete or was never done, the FDA should require an explanation.

- Per action 1.1, the FDA intends to review and update and/or finalize relevant industry guidance related to enhancing subgroup representation in clinical trials, subgroup analysis, and sharing data and results. We believe updating existing guidance can be helpful, but stronger enforcement of FDA's existing authority to require the reporting and analysis of subgroup information is needed more. We recommend issuing specific FDA guidance outlining the penalties and consequences of non-compliance to this existing mandate.

We also applaud the FDA for finalizing its guidance on the *Evaluation of Sex-Specific Data in Medical Device Clinical Studies*. The action plan indicates that FDA plans to incorporate these recommendations into reviewer templates and staff training. We agree that this is a logical and important next step. Additionally, we are pleased to note that the FDA plans to begin drafting guidance on the analysis and reporting of ethnicity, race, and age in medical device studies. We look forward to commenting on the draft guidance and hope the FDA will release it as soon as possible.

- Per recommendation 1.2, the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) plan to revise effectiveness guidance and will consider developing safety guidance to clarify the inclusion of information in medical product applications, particularly as it relates to subgroup analyses. Current FDA regulations already require that demographic data be presented in marketing applications. However, there remains a significant loophole in this criteria. Any demographic subset information that a sponsor mentions in its application – regardless of how minimal or insignificant – meet the FDA requirement to conduct subgroup analysis, even if there was not enough data for *meaningful* analysis.[1] This practice is not in keeping with the intent of the requirement and does not add to the usefulness of the data. Enhanced subgroup analysis can only be achieved if FDA issues clear and specific guidance requiring subgroup-specific analyses for primary safety and efficacy endpoints. In other words, in order for revised guidance to be helpful and result in the improved quality of these analyses, FDA must clarify in its guidance that *meaningful* subgroup analyses must be conducted and then this guidance must be enforced.

- In section 1.4, FDA's plans to revise the MedWatch forms to enable standardized collection of demographic information related to possible adverse events are commendable. While standardized collection of data through MedWatch is critical, we remain concerned that patients with limited English proficiency will still have difficulty reporting adverse events unless the form is available in additional languages. We urge the FDA to translate the online MedWatch forms into languages other than English.

  Also in section 1.4, the FDA has committed to strengthening its post-market surveillance systems to make better use of post-approval data once products are widely in use. Although we do not believe that post-market surveillance should be a substitute for pre-approval demographic subgroup analyses for safety and efficacy, better post-market surveillance is certainly critical. FDA must stringently enforce provisions requiring sponsors to conduct the needed post-market studies. Additionally, the results from the post-market studies must be made readily available and analyzed according to relevant subgroup criterion and be accessible online to clinicians, researchers and patients.

[1] As FDA said in its August 2013 report on the "*Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products*": "Although there is no statutory or regulatory requirement to include demographic subgroups as participants in clinical trials, FDA guidance documents encourage, and regulations clearly require, presentation and inclusion of analysis of demographic data in marketing applications [emphasis added]". Yet the report made clear that FDA makes a distinction between the inclusion of subset analyses information and the provision of actual data sufficient to detect subgroup effects: "Inclusion did not necessarily mean that that data on patient subgroups was sufficient for meaningful analysis or to detect relevant subgroup effects."

- Finally, in section 1.5, FDA laid out plans for the OWH and OMH to continue supporting research to further our understanding of when and why sex, race and ethnicity, and age differences exist. We are very supportive of additional research to better understand issues surrounding recruitment, participation and outcome analysis of subgroup populations so that we can apply these learnings to reducing health disparities.

Priority 2: Improving Participation in Clinical Trials

We are disappointed that the Action Plan does not require representative inclusion of women, minorities and elderly in clinical trials and that most of the plan's actions are focused on phase III trials. However, we appreciate that FDA recognizes the need to achieve greater diversity in trial participation and has laid out a number of strategies for encouraging better participation.

- In section 2.1, the OMH plans to work with the Institute of Medicine to convene a meeting of experts next year to better understand barriers to minority participation in clinical trials. Much work has already been done to both identify the barriers and to identify strategies or best practices that have proven effective in improving representation of minorities. Therefore, we recommend that the FDA establish an Advisory Group on Underrepresented Populations in Clinical Research that would monitor contemporary barriers to participation in clinical trials on an ongoing basis, research those barriers, and make recommendations for addressing them. The 2015 meeting would provide an opportunity to supplement the work of the Advisory Group and seek input from all stakeholders.

- We support the FDA's plan in section 2.2 to work with industry to ensure the appropriate use of exclusion criteria. As the Action Plan points out, elimination of unnecessary exclusions (such as automatically excluding anyone over age 65 or 75) from trial protocols will help to ensure that new products are being tested in a population that more closely resembles the patients who will ultimately be using them. Also, since women live longer than men, this will result in their greater inclusion, especially in cardiovascular trials. We intend to monitor this issue moving forward.

- Under section 2.3 of the plan, we support FDA's plans for collaboration with the National Institutes of Health (NIH), industry, and other stakeholders to broaden diversity in research. The FDA's establishment of a joint working group with NIH on inclusion policies, practices, and challenges is well timed with NIH's changing policies on preclinical research. We hope this working group will lead to the elimination of unnecessary exclusions and the adoption of strategies to achieve greater diversity in both industry-funded and NIH-funded trials, as well as to the inclusion or better representation of women, minorities and the elderly in the earlier phases of clinical research on dosing and efficacy.

  We also support OWH efforts to collaborate with the NIH's Office of Research on Women's Health on a national campaign on the importance of women's participation in clinical trials, and our organizations look forward to partnering with you on this education effort.

- 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, minorities, and the elderly in trials.

- Finally, in section 2.4, FDA plans to explore various ways it can use its communication channels to encourage clinical trial participation, such as distributing a new patient brochure and issuing an FDA Consumer Update. We strongly encourage the FDA to engage with stakeholders to ensure wider dissemination of these materials. Further, we urge the FDA to develop a more specific plan describing how communications with underserved populations will be improved, including through expansion of translation and health literacy initiatives.

Priority 3: Greater Transparency of Data

Finally, collecting and analyzing subgroup data will only be helpful if information is shared with public and health professionals in a manner that is easily accessible and understandable for those making treatment decisions. We are pleased that FDA outlined a number of strategies and actions that it intends to take to make demographic subgroup data more available and transparent.

- First, in section 3.1, CDER and CBER intend to post demographic information for new drugs and biologics on a special new web page, and likewise the FDA plans to explore similar user-friendly ways of posting demographic information for medical devices. Our preference continues to be that product labeling include subgroup information but we are pleased that the Action Plan acknowledges that under the current method such information isn't very accessible to consumers and practitioners. We agree with the plan to pull this information out of the review packages and Summaries of Safety and Effectiveness Data (SSEDs) and make it available on a web page developed specifically for this purpose. FDA should move forward with the initiative for devices, similar to what it has planned for drugs and biologics. Over time, this web site should be expanded to retroactively include information on products already on the market.

- Given our support for including significant demographic subgroup information in the labeling, we are also pleased that FDA indicates in section 3.2 that it plans to work with stakeholders to explore potential methods for communicating meaningful information through the product labeling. We hope this exploration process will lead to inclusion of improved, consistent information on a product's safety and efficacy in women, minorities, and the elderly in the labeling and use instructions.

- We also applaud the FDA for planning in section 3.4 to establish an internal FDA steering committee to oversee implementation of the Action Plan implementation and to report on the status of implementation on the FDA's Section 907 web page. The FDA should provide information about steering committee members and a mechanism to communicate with the committee, such as through the Section 907 webpage. We had 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. Nevertheless this steering committee is a positive step to ensure that the action plan steps actually get implemented, and we recommend that the steering committee quickly establish specific metrics that can be used to assess the implementation and outcomes of the Action Plan. While we have every intention of participating in the public workshop in 18 months, we feel it is important to be able to view implementation progress in an ongoing manner in order for the meeting to be effective in its evaluation of where the FDA is with the 27 Action Plan steps.

Conclusion

In closing, we appreciate the FDA's work in preparing this Action Plan, and we are eager to work with FDA on its implementation. The ultimate success of this plan will depend upon its timely, thorough execution and on its enforcement. 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 that women, minorities, and the elderly currently face.

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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; Coco Jervis, Program Director at the National Women's Health Network, at 202-682-2640 or cjervis@nwhn.org; Martha Nolan, Vice President, Public Policy at the Society for Women's Health Research (SWHR), at 202-496-5007 or Martha@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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